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(54) **PHENYLACETAMIDES BEING FLT3 INHIBITORS**

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This patent is subject to a terminal disclaimer.

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546/118

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See application file for complete search history.

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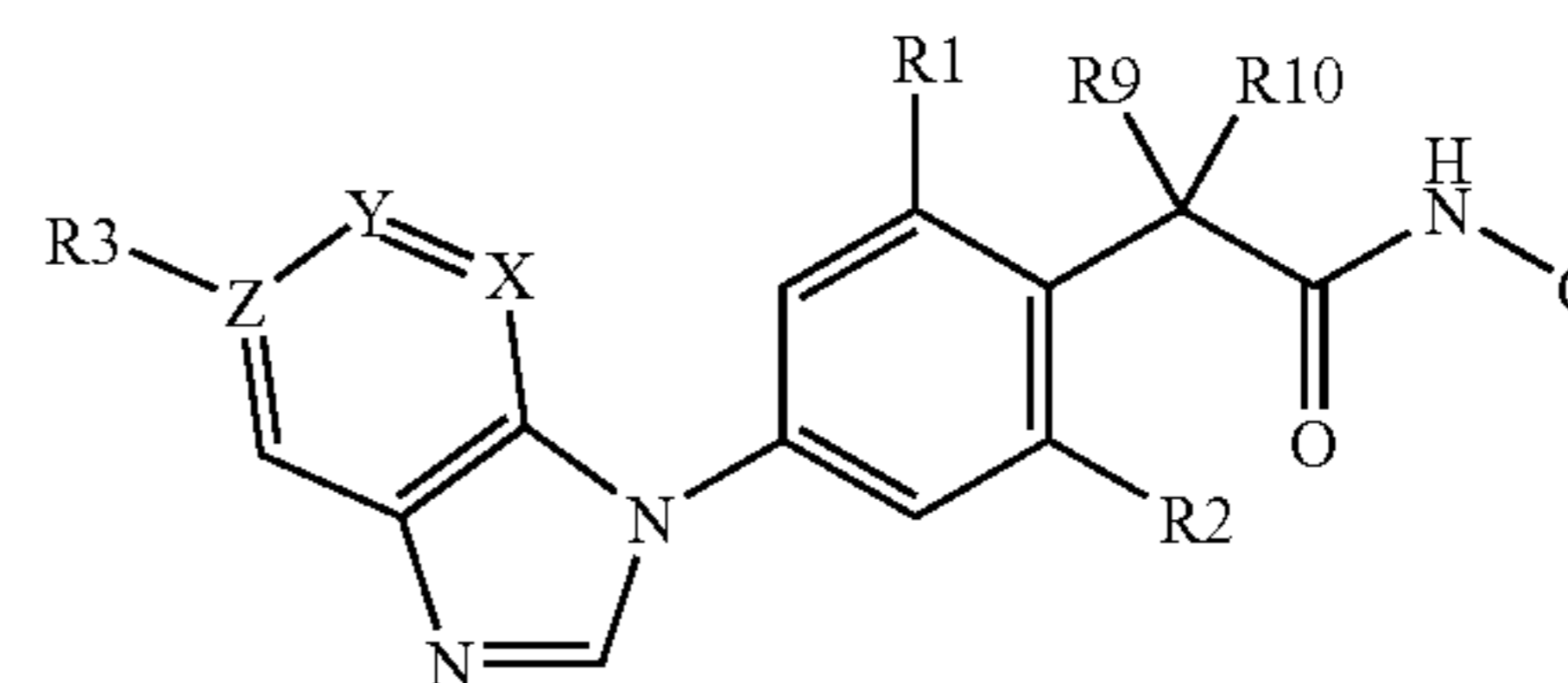
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(57) **ABSTRACT**

Compounds of formula



wherein the residues R1, R2, R3, R9, R10 and Q and X, Y and Z are as defined in the specification, salts thereof; their use, methods of their use, processes for their production, pharmaceutical compositions comprising them, their combinations with second drug substances and the use thereof and the like. The compounds are protein kinase inhibitors and can be used for the treatment of diseases mediated by protein kinase inhibitors, e.g. for the treatment of various proliferative diseases.

4 Claims, No Drawings

PHENYLACETAMIDES BEING FLT3 INHIBITORS

This application is the National Stage of Application No. PCT/EP2007/060937, filed on Oct. 10, 2007, which claims benefit under 35 U.S.C. §119(a)-(d) or (f) or 365(b) of EP Application No. 06122388.9, filed Oct. 16, 2006, the contents of which are incorporated herein by reference in their entirety.

The present invention relates to phenylacetyl amide derivatives, their use as protein kinase inhibitors, new pharmaceutical formulations comprising said compounds, said compounds for use in the diagnostic or therapeutic treatment of animals, especially humans, their use in the treatment of diseases or for the manufacture of pharmaceutical formulations useful in the treatment of diseases that respond to modulation of protein kinases, a pharmaceutical formulation e.g. useful in the treatment of diseases that respond to modulation of protein kinase comprising said compound, methods of treatment comprising administration of said compounds to a warm-blooded animal, and/or processes for the manufacture of said compounds.

BACKGROUND OF THE PRESENT INVENTION

Among the protein kinases, receptor-type kinases and non-receptor-type kinases can be distinguished, as well as tyrosine and serine/threonine kinases. Depending on their localization, nuclear, cytoplasmic and membrane-associated kinases can be distinguished. Membrane-associated tyrosine kinases often are at the same time receptors for growth factors.

Protein kinases (PKs) are enzymes which catalyze the phosphorylation of specific serine, threonine or tyrosine residues in cellular proteins. These post-translational modifications of substrate proteins act as molecular switch as a step in regulating cell proliferation, activation and/or differentiation. Aberrant or excessive or more generally inappropriate PK activity has been observed in several disease states including benign and malignant proliferative disorders. In many cases, it has been possible to treat diseases *in vitro* and in many cases *in vivo*, such as proliferative disorders, by making use of PK inhibitors.

The number of protein kinase inhibitors is high. In addition, a multitude of proliferative and other PK-related diseases exists. In some cases, the treated diseases develop resistance against therapeutics. Also, in some patients very specific treatments are required. Thus, there is a continuous need to provide new classes of compounds that are useful as PK inhibitors and consequently in the treatment of these Protein Tyrosine Kinase (PTK) related diseases in order to add to the present equipment of available drugs. What is required are new classes of pharmaceutically advantageous PK inhibiting compounds.

The Philadelphia Chromosome is a hallmark for chronic myelogenous leukaemia (CML) and carries a hybrid gene that contains N-terminal exons of the *bcr* gene and the major C-terminal part (exons 2-11) of the *c-abl* gene. The gene product is a 210 kD protein (p210 Bcr-Abl). The Abl-part of the Bcr-Abl protein contains the abl-tyrosine kinase which is tightly regulated in the wild type *c-abl*, but constitutively activated in the Bcr-Abl fusion protein. This deregulated tyrosine kinase interacts with multiple cellular signaling pathways leading to transformation and deregulated proliferation of the cells (Lugo et al., *Science* 247, 1079 [1990]). Mutant forms of the Bcr-Abl protein have also been identified. A detailed review of Bcr-Abl mutant forms has been published (Cowan-Jones et al, *Mini Reviews in Medicinal*

Chemistry, 2004, 4 285-299). Treatment by inhibitors of *c-abl* and its mutations is useful against leukemias, e.g. AML and CML.

c-Kit is a tyrosine kinase receptor which belongs to the PDGF receptor family and becomes activated upon binding of its ligand SCF (stem-cell factor). The expression pattern of *c-kit* has been studied e.g. in a panel of different primary solid tumors. A strong expression of *kit* could be found *inter alia* in sarcoma, gastrointestinal stromal tumors (GIST), seminoma and carcinoids (Weber et al., *J. Clin. Oncol.* 22(14S), 9642 (2004)). GIST are non-epithelial tumors, diagnostically separate from other common forms of bowel cancer. Many occur in the stomach, less in the small intestine and still less in the esophagus. Dissemination to the liver, omentum and peritoneal cavity can be observed. GISTs probably arise from Interstitial Cajal Cells (ICC) which normally form part of the autonomic nervous system of the intestine and take part in the control of motility. Most (50 to 80%) of GISTs arise due to *c-kit* gene mutation. In the gut, a staining positive for *c-kit*/CD117 is likely to be a GIST. Mutations of *c-kit* can make *c-kit* function independent of activation by SCF, leading to a high cell division rate and possibly genomic instability. Also in mast cell tumors aberrations of *c-kit* could be observed, as well as in mastocytosis and associated myeloproliferative syndrome and Urticaria Pigmentosa. An expression and/or aberrations of *c-kit* can also be found in acute myeloid anemia (AML) and malignant lymphomas. A *c-kit* expression can also be demonstrated in small cell bronchial carcinoma, seminomas, dysgerminomas, testicular intraepithelial neoplasias, melanomas, mamma carcinomas, neuroblastomas, Ewing sarcoma, some soft part sarcomas as well as papillary/follicular thyroid carcinoma (see Schütte et al., *innovartis March* 2001). Inherited mutations of the RET (rearranged during transfection) proto-oncogene are e.g. known to be tumorigenic in patients with multiple endocrine neoplasia type 2 (MEN 2) which may lead to pheochromocytoma, medullary thyroid carcinoma and parathyroid hyperplasia/adenoma (see Huang et al., *Cancer Res.* 60, 6223-6 (2000)). In patients with MEN 2, germ-line mutations of RET and sometimes duplication of a mutant RET allele in trisomy 10 or loss of the wild type RET allele are commonly identified and believed to be activating, i.e. causing ligand-independent dimerization of the receptor.

Platelet derived growth factor receptors such as PDGFR- α and - β are also trans-membrance tyrosine kinase receptors. Upon binding of the ligand that is formed from two A, two B or in heterodimers from one A and one B chain (PDGF-A, PDGF-B or PDGF-AB), the receptor dimerizes and its tyrosine kinase is activated. This leads to downstream signaling and thus may support tumor growth. Mutations in this gene allow for receptor activation independent of ligand binding and appear to be driving forces in oncogenesis (see GIST may also be characterized by activating mutations in the platelet-derived growth factor-receptor- α (PDGFR α) gene. An expression of PDGF, the growth factor that activates PDGFR, was observed in a number of different tumor cell lines, *inter alia* in mamma, colon, ovarian, prostate carcinoma, sarcoma and glioblastomas cell lines. Among the tumors, brain tumors and prostate carcinoma (including adenocarcinomas and bone metastasis) have found special interest. Interesting data also exist regarding malignant gliomas (anaplastic astrocytomas/glioblastomas). Interesting pre-clinical data have also been obtained in the treatment of Dermatofibrosarcoma protuberans, a soft part tumor which is genetically characterized by a fusion of the collagen-type I α 1 (COL1A1) with the PDGF-A

3

VEGFRs (vascular endothelial growth factor receptors) are known to be involved in the control of the onset of angiogenesis. As especially solid tumors depend on good blood supply, inhibition of VEGFRs and thus angiogenesis is under clinical investigation in the treatment of such tumors, showing promising results. VEGF is also a major player in leukemias and lymphomas and highly expressed in a variety of solid malignant tumors, correlating well with malignant disease progression. Examples of tumor diseases with VEGFR-2 (KDR) expression are lung carcinomas, breast carcinomas, Non Hodgkin's lymphomas, ovarian carcinoma, pancreatic cancer, malignant pleural mesothelioma and melanoma. In addition to its angiogenic activity, the ligand of VEGFR, VEGF, may promote tumor growth by direct pro-survival effects in tumor cells. Various other diseases are associated with deregulated angiogenesis, e.g. as mentioned below.

FLT3 is a member of the type III receptor tyrosine kinase (RTK) family. FLT3 (fms-like tyrosine kinase) is also known as FLk-2 (fetal liver kinase 2). Aberrant expression of the FLT3 gene has inter alia been documented in both adult and childhood leukemias including acute myeloid leukemia (AML), AML with trilineage myelodysplasia (AML/TMDS), acute lymphoblastic leukemia (ALL), and myelodysplastic syndrome (MDS), as well as MLL (mixed-lineage leukemia). Activating mutations of the FLT3 receptor have been found in about 35% of patients with acute myeloblastic leukemia (AML), and are associated with a poor prognosis. The most common mutation involves an in-frame duplication within the juxtamembrane domain, with an additional 5-10% of patients having a point mutation at asparagine 835. Both of these mutations are associated with constitutive activation of the tyrosine kinase activity of FLT3, and result in proliferation and viability signals in the absence of ligand. Patients expressing the mutant form of the receptor have been shown to have a decreased chance for cure. Thus, there is accumulating evidence for a role for hyperactivated (mutated) FLT3 kinase activity in human leukemias and myelodysplastic syndrome.

Angiopoietins (ligands of Tie-2) and Tie-2 are involved in vessel stabilization and vascular remodeling. It is known that Tie-2 is activated by one of its ligands, angiopoietin-1, which is antagonized by a second ligand, angiopoietin-2 (ang2). In sites where angiogenesis takes place, the antagonist ang2 is up-regulated.

It is a problem to be solved by the present invention to provide new inhibitors of protein kinases, especially one or more of those just described, and to thus add new compounds to the few available compounds that exist so far.

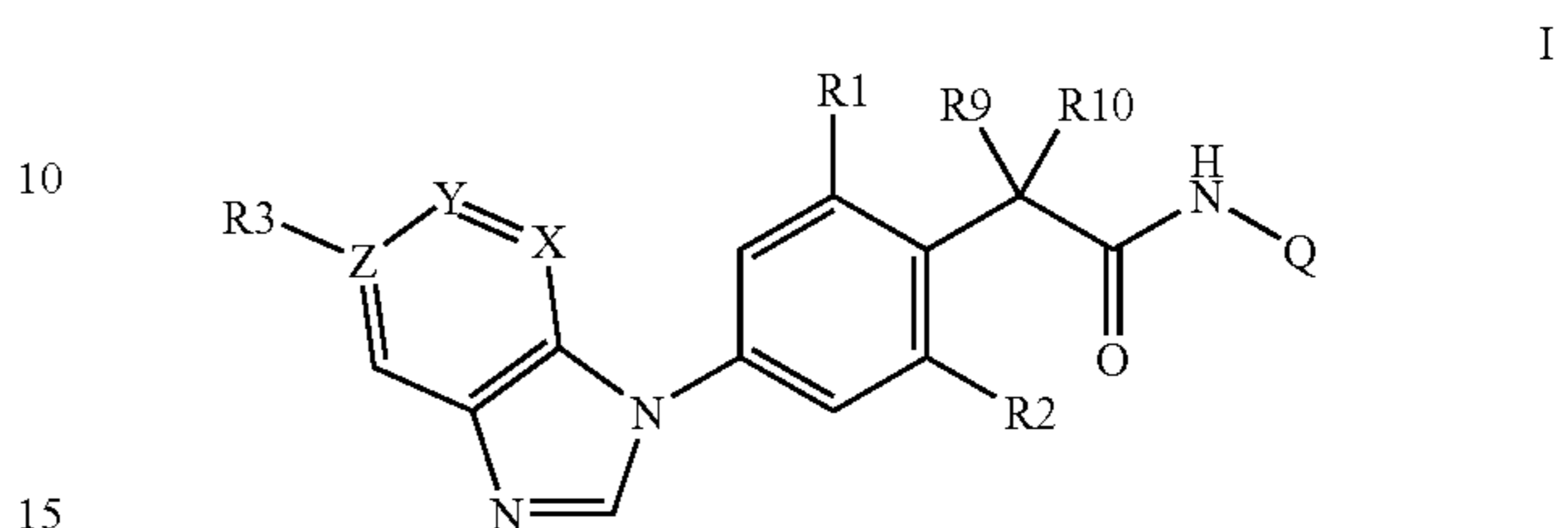
GENERAL DESCRIPTION OF THE PRESENT INVENTION

It has now been found that the compounds of formula I show inhibition of a number of protein kinases. The compounds of formula I, described below in more detail, especially show inhibition of one or more of the following protein kinases: tie-2, preferably c-Abl, Bcr-Abl, c-Kit, the RET proto-oncogene, Platelet-derived Growth Factor Receptors (PDGFRs), FLT3 receptor kinase and the Vascular Endothelial Growth Factor Receptors (VEGFRs) such as in particular VEGFR2. The compounds of formula I further also inhibit mutants of said kinases. In view of these activities, the compounds of formula I can be used for the treatment of diseases related to especially aberrant or excessive activity of such types of kinases, especially those mentioned.

4

DETAILED DESCRIPTION OF THE PRESENT INVENTION

In one aspect the present invention provides a compound of formula



wherein

(i) each of R1 and R2, independently of the other, is selected from the group consisting of hydrogen, halo and C₁-C₇-alkyl;

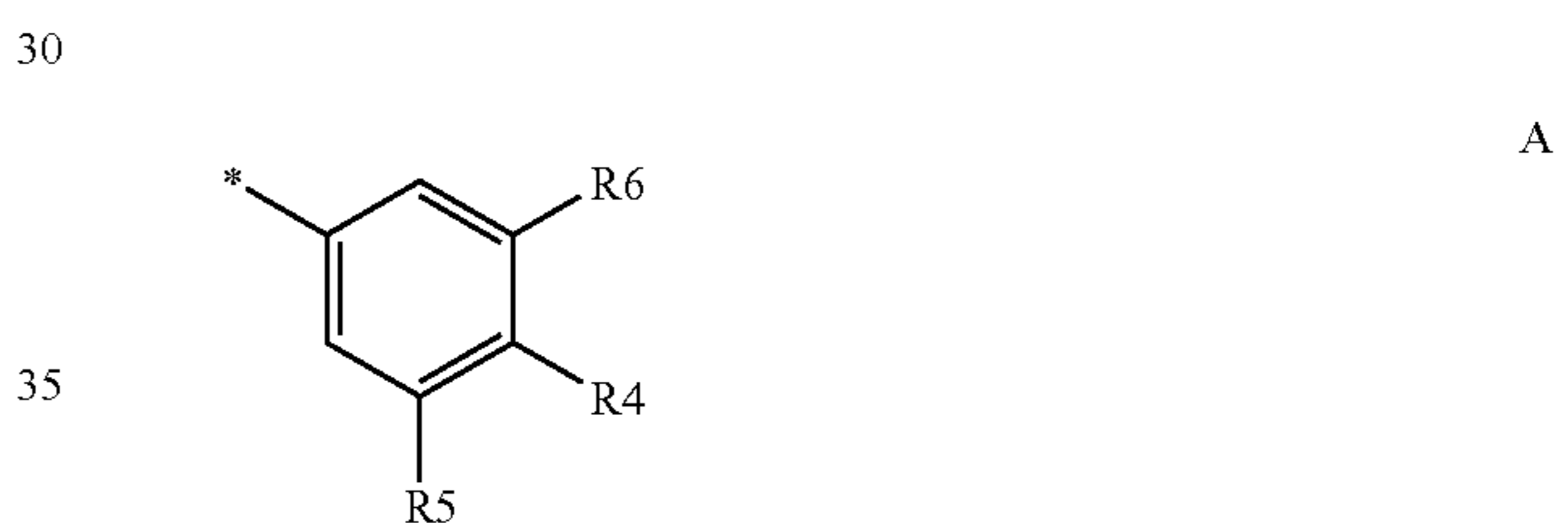
R3 is absent if Z is nitrogen or, if Z is C (carbon), is hydrogen, unsubstituted or substituted aryl or unsubstituted or substituted heterocyclyl;

X is N (nitrogen) or CH (hydrogen-substituted carbon),

Y is CH or N,

Z is C or N, and

Q is a group of the formula



wherein

(a) R4 is hydrogen, halo, unsubstituted or substituted amino, unsubstituted or substituted aryl, unsubstituted or substituted heterocyclyl bound via a ring atom other than nitrogen, unsubstituted or substituted cycloalkyl, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl or unsubstituted or substituted alkynyl;

R5 is 1-methyl-piperidin-4-yloxy), 1-methyl-piperidin-4-yl, 2-dimethylamino-ethyl or 4-ethyl-piperazin-1-yl; and

R6 is hydrogen, unsubstituted or substituted cycloalkyl or unsubstituted or (preferably) substituted alkyl; or

(b) R4 is 1-methyl-piperidin-4-ylmethyl), 1-ethyl-piperidin-4-ylmethyl, 1-methyl-piperidin-4-yloxy or 1-isopropyl-piperidin-4-ylmethyl;

R5 is hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted amino, unsubstituted or substituted aryl or unsubstituted or substituted heterocyclyl; and

R6 is hydrogen, unsubstituted or substituted cycloalkyl or unsubstituted or (preferably) substituted alkyl;

where the asterisk * in formula (A) marks the bond through which the moiety is bound to the NH of the amide group in formula I; and

either each of R9 and R10, independently of the other, is selected from the group consisting of hydrogen, hydroxyl and C₁-C₇-alkyl; or

5

R9 and R10 together represent oxo; or

R1 and R9 together form a group $-\text{C}(\text{O})-\text{CH}_2-$ or $-\text{CH}_2-\text{CH}_2-$, R2 is selected from the group consisting of hydrogen, halo and C_1-C_7 -alkyl, and R10 represents hydrogen; or

(ii) which is selected from the group consisting of

2-(4-Benzoimidazol-1-yl-phenyl)-N-[4-(4-isopropyl-piperazin-1-ylmethyl)-3-trifluoromethyl-phenyl]-acetamide,

2-(4-Benzoimidazol-1-yl-phenyl)-N-(4-diethylaminomethyl-3-trifluoromethyl-phenyl)-acetamide,

2-(4-Benzoimidazol-1-yl-phenyl)-N-(4-pyrrolidin-1-ylmethyl-3-trifluoromethyl-phenyl)-acetamide,

2-(2-Chloro-4-imidazo[4,5-b]pyridin-3-yl-phenyl)-N-(4-diethylaminomethyl-3-trifluoromethyl-phenyl)-acetamide,

2-(2-Chloro-4-imidazo[4,5-b]pyridin-3-yl-phenyl)-N-(4-pyrrolidin-1-ylmethyl-3-trifluoromethyl-phenyl)-acetamide,

N-[3-(4-Ethyl-piperazin-1-ylmethyl)-5-trifluoromethyl-phenyl]-2-(4-imidazo[4,5-b]pyridin-3-yl-phenyl)-acetamide,

N-(3-Diethylaminomethyl-5-trifluoromethyl-phenyl)-2-(4-imidazo[4,5-b]pyridin-3-yl-phenyl)-acetamide,

2-(4-Benzoimidazol-1-yl-phenyl)-N-(3-diethylaminomethyl-5-trifluoromethyl-phenyl)-acetamide

2-(4-Imidazo[4,5-b]pyridin-3-yl-phenyl)-N-[3-(4-methyl-imidazol-1-yl)-5-trifluoromethyl-phenyl]-acetamide,

2-(4-Imidazo[4,5-b]pyridin-3-yl-2-methyl-phenyl)-N-[3-(4-methyl-imidazol-1-yl)-5-trifluoromethyl-phenyl]-acetamide,

2-(4-Imidazo[4,5-b]pyridin-3-yl-2-methyl-phenyl)-N-[3-(4-methyl-piperazin-1-yl)-5-trifluoromethyl-phenyl]-acetamide,

N-[3-(4-Ethyl-piperazin-1-ylmethyl)-5-trifluoromethyl-phenyl]-2-(4-imidazo[4,5-b]pyridin-3-yl-2-methyl-phenyl)-acetamide,

2-(2-Chloro-4-imidazo[4,5-b]pyridin-3-yl-phenyl)-N-[3-(4-methyl-imidazol-1-yl)-5-trifluoromethyl-phenyl]-acetamide,

2-(4-Benzoimidazol-1-yl-phenyl)-N-[3-(4-methyl-imidazol-1-yl)-5-trifluoromethyl-phenyl]-acetamide,

2-(4-Benzoimidazol-1-yl-phenyl)-N-[3-(4-ethyl-piperazin-1-ylmethyl)-5-trifluoromethyl-phenyl]-acetamide, and

2-(4-Imidazo[4,5-b]pyridin-3-yl-2-methyl-phenyl)-N-[4-(1-methyl-piperidin-4-ylmethyl)-3-trifluoromethyl-phenyl]-acetamide.

In a compound of formula I preferably

X is C or NH;

Y is CH;

Z is C;

R1 is H;

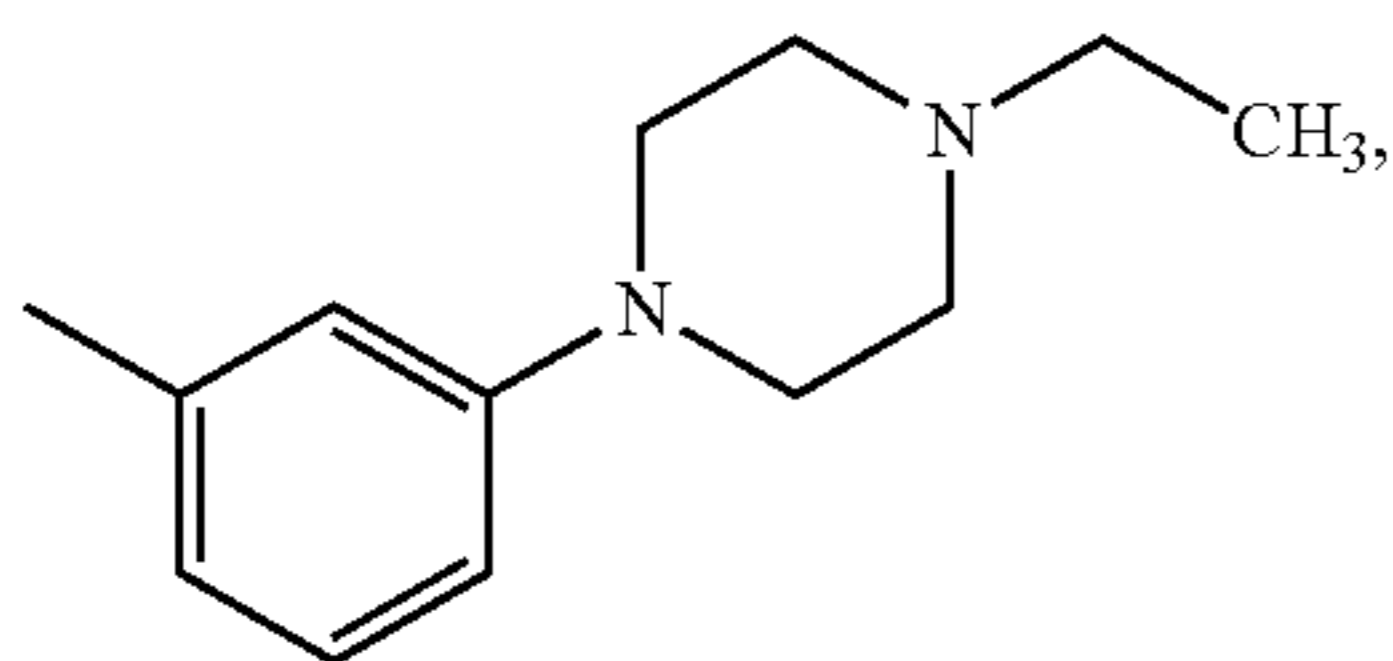
R2 is hydrogen, halo or C_1-C_7 -alkyl, such as methyl,

R3 is H;

R9 is H;

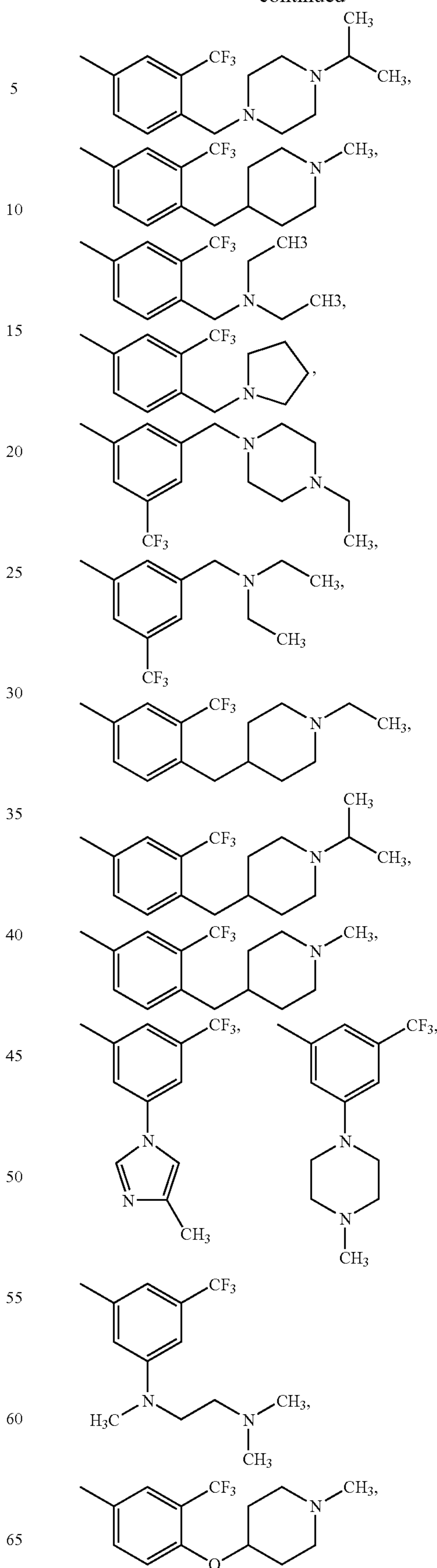
R10 is H;

Q is selected from groups consisting of the group

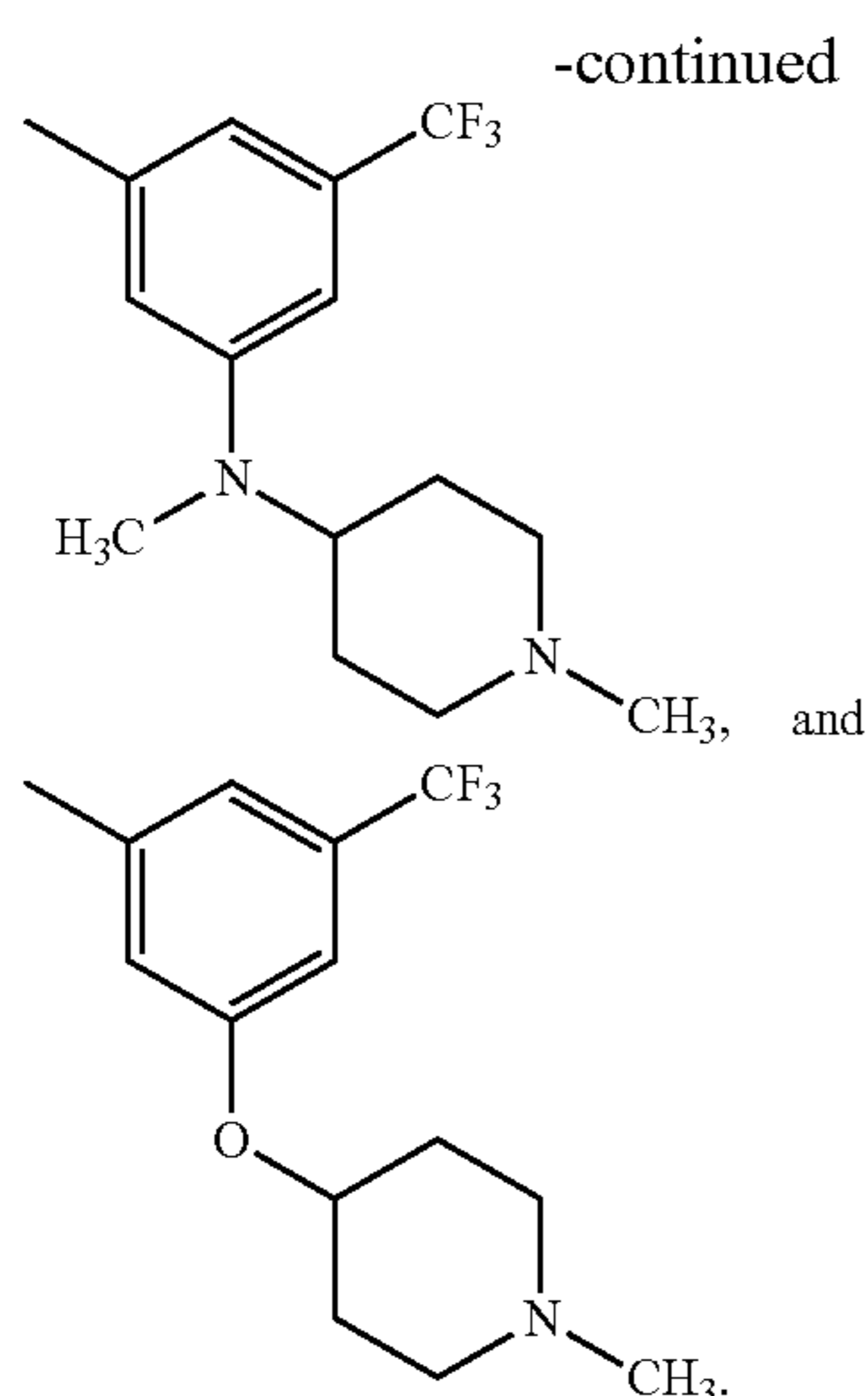


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7



In a compound of formula I each group of substituents indicated may be a preferred group, independently from the other groups defined; and each single substituent indicated may be a preferred substituent, independently from the other substituents defined.

In another aspect the present invention provides a compound selected from the group consisting of

N-[3-(4-Ethyl-piperazin-1-yl)-phenyl]-2-(4-imidazo[4,5-b]pyridin-3-yl-phenyl)-acetamide,

2-(4-Benzoimidazol-1-yl-phenyl)-N-[4-(4-isopropyl-piperazin-1-ylmethyl)-3-trifluoromethyl-phenyl]-acetamide,

2-(4-Imidazo[4,5-b]pyridin-3-yl-phenyl)-N-[4-(1-methyl-piperidin-4-ylmethyl)-3-trifluoromethyl-phenyl]-acetamide,

2-(4-Benzoimidazol-1-yl-phenyl)-N-(4-diethylaminomethyl-3-trifluoromethyl-phenyl)-acetamide),

2-(4-Benzoimidazol-1-yl-phenyl)-N-(4-pyrrolidin-1-ylmethyl-3-trifluoromethyl-phenyl)-acetamide,

2-(2-Chloro-4-imidazo[4,5-b]pyridin-3-yl-phenyl)-N-(4-diethylaminomethyl-3-trifluoromethyl-phenyl)-acetamide,

2-(2-Chloro-4-imidazo[4,5-b]pyridin-3-yl-phenyl)-N-(4-pyrrolidin-1-ylmethyl-3-trifluoromethyl-phenyl)-acetamide,

N-[3-(4-Ethyl-piperazin-1-ylmethyl)-5-trifluoromethyl-phenyl]-2-(4-imidazo[4,5-b]pyridin-3-yl-phenyl)-acetamide,

N-(3-Diethylaminomethyl-5-trifluoromethyl-phenyl)-2-(4-imidazo[4,5-b]pyridin-3-yl-phenyl)-acetamide,

2-(4-Benzoimidazol-1-yl-phenyl)-N-(3-diethylaminomethyl-5-trifluoromethyl-phenyl)-acetamide,

N-[4-(1-Ethyl-piperidin-4-ylmethyl)-3-trifluoromethyl-phenyl]-2-(4-imidazo[4,5-b]pyridin-3-yl-phenyl)-acetamide,

2-(4-Benzoimidazol-1-yl-phenyl)-N-[4-(1-ethyl-piperidin-4-ylmethyl)-3-trifluoromethyl-phenyl]-acetamide,

2-(2-Chloro-4-imidazo[4,5-b]pyridin-3-yl-phenyl)-N-[4-(1-ethyl-piperidin-4-ylmethyl)-3-trifluoromethyl-phenyl]-acetamide,

2-(2-Chloro-4-imidazo[4,5-b]pyridin-3-yl-phenyl)-N-[4-(1-isopropyl-piperidin-4-ylmethyl)-3-trifluoromethyl-phenyl]-acetamide,

2-(4-Imidazo[4,5-b]pyridin-3-yl-phenyl)-N-[4-(1-isopropyl-piperidin-4-ylmethyl)-3-trifluoromethyl-phenyl]-acetamide,

2-(4-Benzoimidazol-1-yl-phenyl)-N-[4-(1-isopropyl-piperidin-4-ylmethyl)-3-trifluoromethyl-phenyl]-acetamide,

2-(2-Chloro-4-imidazo[4,5-b]pyridin-3-yl-phenyl)-N-[4-(1-methyl-piperidin-4-ylmethyl)-3-trifluoromethyl-phenyl]-acetamide,

8

2-(4-Benzoimidazol-1-yl-phenyl)-N-[4-(1-methyl-piperidin-4-ylmethyl)-3-trifluoromethyl-phenyl]-acetamide,

2-(4-Imidazo[4,5-b]pyridin-3-yl-phenyl)-N-[3-(4-methyl-imidazol-1-yl)-5-trifluoromethyl-phenyl]-acetamide,

2-(4-Imidazo[4,5-b]pyridin-3-yl-2-methyl-phenyl)-N-[3-(4-methyl-imidazol-1-yl)-5-trifluoromethyl-phenyl]-acetamide,

2-(4-Imidazo[4,5-b]pyridin-3-yl-2-methyl-phenyl)-N-[3-(4-methyl-piperazin-1-yl)-5-trifluoromethyl-phenyl]-acetamide,

N-[3-(4-Ethyl-piperazin-1-ylmethyl)-5-trifluoromethyl-phenyl]-2-(4-imidazo[4,5-b]pyridin-3-yl-2-methyl-phenyl)-acetamide,

2-(2-Chloro-4-imidazo[4,5-b]pyridin-3-yl-phenyl)-N-[3-(4-methyl-imidazol-1-yl)-5-trifluoromethyl-phenyl]-acetamide,

2-(4-Benzoimidazol-1-yl-phenyl)-N-[3-(4-methyl-imidazol-1-yl)-5-trifluoromethyl-phenyl]-acetamide,

2-(4-Benzoimidazol-1-yl-phenyl)-N-[3-(4-ethyl-piperazin-1-ylmethyl)-5-trifluoromethyl-phenyl]-acetamide,

2-(4-Imidazo[4,5-b]pyridin-3-yl-2-methyl-phenyl)-N-[4-(1-methyl-piperidin-4-ylmethyl)-3-trifluoromethyl-phenyl]-acetamide,

2-(2-Chloro-4-imidazo[4,5-b]pyridin-3-yl-phenyl)-N-[3-[(2-dimethylamino-ethyl)-methyl-amino]-5-trifluoromethyl-phenyl]-acetamide,

N-[3-[(2-Dimethylamino-ethyl)-methyl-amino]-5-trifluoromethyl-phenyl]-2-(4-imidazo[4,5-b]pyridin-3-yl-2-methyl-phenyl)-acetamide,

N-[3-[(2-Dimethylamino-ethyl)-methyl-amino]-5-trifluoromethyl-phenyl]-2-(4-imidazo[4,5-b]pyridin-3-yl-phenyl)-acetamide,

2-(4-Benzoimidazol-1-yl-phenyl)-N-[3-[(2-dimethylamino-ethyl)-methyl-amino]-5-trifluoromethyl-phenyl]-acetamide,

2-(4-Benzoimidazol-1-yl-phenyl)-N-[4-(1-methyl-piperidin-4-yloxy)-3-trifluoromethyl-phenyl]-acetamide,

2-(4-Imidazo[4,5-b]pyridin-3-yl-phenyl)-N-[4-(1-methyl-piperidin-4-yloxy)-3-trifluoromethyl-phenyl]-acetamide,

2-(4-Imidazo[4,5-b]pyridin-3-yl-2-methyl-phenyl)-N-[4-(1-methyl-piperidin-4-yloxy)-3-trifluoromethyl-phenyl]-acetamide,

2-(2-Chloro-4-imidazo[4,5-b]pyridin-3-yl-phenyl)-N-[4-(1-methyl-piperidin-4-yloxy)-3-trifluoromethyl-phenyl]-acetamide,

2-(2-Chloro-4-imidazo[4,5-b]pyridin-3-yl-phenyl)-N-[3-[methyl-(1-methyl-piperidin-4-yl)-amino]-5-trifluoromethyl-phenyl]-acetamide,

2-(4-Imidazo[4,5-b]pyridin-3-yl-2-methyl-phenyl)-N-[3-[methyl-(1-methyl-piperidin-4-yl)-amino]-5-trifluoromethyl-phenyl]-acetamide,

2-(4-Imidazo[4,5-b]pyridin-3-yl-phenyl)-N-[3-[methyl-(1-methyl-piperidin-4-yl)-amino]-5-trifluoromethyl-phenyl]-acetamide,

2-(4-Benzoimidazol-1-yl-phenyl)-N-[3-[methyl-(1-methyl-piperidin-4-yl)-amino]-5-trifluoromethyl-phenyl]-acetamide,

2-(2-Chloro-4-imidazo[4,5-b]pyridin-3-yl-phenyl)-N-[3-(1-methyl-piperidin-4-yloxy)-5-trifluoromethyl-phenyl]-acetamide,

2-(4-Imidazo[4,5-b]pyridin-3-yl-2-methyl-phenyl)-N-[3-(1-methyl-piperidin-4-yloxy)-5-trifluoromethyl-phenyl]-acetamide,

2-(4-Imidazo[4,5-b]pyridin-3-yl-phenyl)-N-[3-(1-methyl-piperidin-4-yloxy)-5-trifluoromethyl-phenyl]-acetamide, and

2-(4-Benzoimidazol-1-yl-phenyl)-N-[3-(1-methyl-piperidin-4-yloxy)-5-trifluoromethyl-phenyl]-acetamide.

Compounds provided by the present invention are herein-after designated as "compound(s) of (according to) the present invention". A compound of the present invention includes a compound in any form, e.g. in free form, in the form of a salt, in the form of a solvate and in the form of a salt and a solvate.

The present invention also relates to a compound of formula I as defined above or below, or a pharmaceutically acceptable salt thereof in the diagnostic or therapeutic treatment of an animal, especially a warm-blooded animal or a human, especially of a disease or disorder that responds to modulation, especially inhibition, of a protein kinase, preferably one or more protein kinases selected from the group consisting of tie-2 and/or more especially PDGFR, VEGFR-2, c-Abl, Flt3, Ret, kit and IGF1R, and/or one or more altered or mutated forms of any one or more of these.

Another embodiment of the invention relates to a pharmaceutical composition comprising a compound of formula I as defined above or below, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient, e.g. carrier material.

Yet another embodiment of the invention relates to the use of a compound of the formula I, or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical composition for the treatment of a disease or disorder that depends on (especially inappropriate) activity of a protein kinase, especially a protein tyrosine kinase, more especially one or more protein kinases selected from the group consisting of tie-2 and/or more especially PDGFR, VEGFR-2, c-Abl, Flt3, Ret and kit, and/or one or more altered or mutated forms of any one or more of these; or the use of said compounds in the treatment of a disease that depends on (especially inappropriate) activity of a protein kinase, especially a protein tyrosine kinase, especially as just defined.

The present invention also relates to a method of treating a kinase dependent and/or proliferative disease comprising administering a compound of the formula I, or a pharmaceutically acceptable salt thereof, to an animal, preferably a warm-blooded animal, especially a human.

DEFINITIONS

Listed below are definitions of various terms used to describe the compounds of the present invention as well as their use and synthesis, starting materials and intermediates and the like. These definitions, either by replacing one, more than one or all general expressions or symbols used in the present disclosure and thus yielding preferred embodiments of the invention, preferably apply to the terms as they are used throughout the specification unless they are otherwise limited in specific instances either individually or as part of a larger group. In other terms: Independently of each other, one or more of the more general expressions may be replaced by the more specific definitions, thus leading to preferred embodiments of the invention.

The term "lower" or "C₁-C₇-" defines a moiety with up to and including maximally 7, especially up to and including maximally 4, carbon atoms, said moiety being branched (one or more times) or straight-chained and bound via a terminal or a non-terminal carbon. Lower or C₁-C₇-alkyl, for example, is

n-pentyl, n-hexyl or n-heptyl or preferably C₁-C₄-alkyl, especially as methyl, ethyl, n-propyl, sec-propyl, n-butyl, isobutyl, sec-butyl, tert-butyl.

Halo or halogen is preferably fluoro, chloro, bromo or iodo, most preferably fluoro, chloro or bromo, if not defined otherwise.

In unsubstituted or substituted aryl, aryl is preferably an unsaturated carbocyclic system of not more than 20 carbon atoms, especially not more than 16 carbon atoms, is preferably mono-, bi- or tri-cyclic, and is unsubstituted or, as substituted aryl, substituted preferably by one or more, preferably up to three, e.g. one or two substituents independently selected from the group consisting of phenyl, naphthyl, phenyl- or naphthyl-lower alkyl, such as benzyl; hydroxy-lower alkyl, such as hydroxymethyl; lower-alkoxy-lower alkyl, (lower-alkoxy)-lower alkoxy-lower alkyl, lower alkanoyl-lower alkyl, halo-lower alkyl, such as trifluoromethyl; phenoxy- or naphthoxy-lower alkyl, phenyl- or naphthyl-lower alkoxy-lower alkyl, such as benzyloxy-lower alkyl; lower alkoxy-carbonyloxy-lower alkyl, such as tert-butoxycarbonyloxy-lower alkyl; phenyl- or naphthyl-lower alkoxy-carbonyloxy-lower alkyl, such as benzyloxycarbonyloxy-lower alkyl; cyano-lower alkyl, lower alkenyl being unsubstituted or substituted by unsubstituted or substituted amino, lower alkynyl, lower alkanoyl, such as acetyl; hydroxy, lower alkoxy, lower-alkoxy-lower alkoxy, (lower-alkoxy)-lower alkoxy-lower alkoxy, phenoxy, naphthoxy, phenyl- or naphthyl-lower alkoxy, such as benzyloxy; amino-lower alkoxy, lower-alkanoyloxy, benzoyloxy, naphthoyloxy, nitro, halo, especially fluoro, chloro, bromo or iodo, amino, mono-di-substituted amino wherein the amino substituents are independently selected from lower alkyl, lower alkanoyl, phenyl, naphthyl, phenyl- and naphthyl-lower alkyl; cyano, carboxy, lower alkoxy carbonyl, e.g. methoxy carbonyl, n-propoxy carbonyl, iso-propoxy carbonyl or tert-butoxycarbonyl; phenyl- or naphthyl-lower alkoxy-carbonyl, such as benzyloxy-carbonyl; lower alkanoyl, benzoyl, naphthoyl, carbamoyl, N-mono- or N,N-disubstituted carbamoyl, such as N-mono- or N,N-di-substituted carbamoyl wherein the substituents are selected from lower alkyl and hydroxy-lower alkyl; amidino, guanidino, ureido, mercapto, lower alkylthio, phenyl- or naphthylthio, phenyl- or naphthyl-lower alkylthio, lower alkyl-phenylthio, lower alkyl-naphthylthio, halogen-lower alkylmercapto, lower alkylsulfinyl, phenyl- or naphthyl-sulfinyl, phenyl- or naphthyl-lower alkylsulfinyl, lower alkyl-phenylsulfinyl, lower alkyl-naphthylsulfinyl, sulfo, lower alkane-sulfonyl, phenyl- or naphthyl-sulfonyl, phenyl- or naphthyl-lower alkylsulfonyl, alkylphenylsulfonyl, halogen-lower alkylsulfonyl, such as trifluoromethanesulfonyl; sulfonamido and benzosulfonamido; where each phenyl or naphthyl (also in phenoxy or naphthoxy) mentioned above as substituent or part of a substituent of substituted aryl is itself unsubstituted or substituted by one or more, e.g. up to three, preferably 1 or 2, substituents independently selected from halo, especially fluoro, chloro, bromo or iodo, halo-lower alkyl, such as trifluoromethyl, hydroxy, lower alkoxy, amino, N-mono- or N,N-di-(lower alkyl, phenyl, naphthyl, phenyl-lower alkyl and/or naphthyl-lower alkyl)amino, nitro, carboxy, lower-alkoxycarbonyl carbamoyl, cyano and/or sulfamoyl.

In unsubstituted or substituted heterocyclyl, heterocyclyl is preferably a heterocyclic radical that is unsaturated, saturated or partially saturated and is preferably a monocyclic or in a broader aspect of the invention bicyclic or tricyclic ring; has 3 to 24, more preferably 4 to 16, most preferably 4 to 10 ring atoms; wherein one or more, preferably one to four, especially one or two carbon ring atoms are replaced by a heteroatom selected from the group consisting of nitrogen, oxygen

and sulfur, the bonding ring preferably having 4 to 12, especially 5 to 7 ring atoms; where heterocyclyl is unsubstituted or substituted by one or more, especially 1 to 3, substituents independently selected from the group consisting of the substituents defined above under "substituted aryl"; and where heterocyclyl is especially a heterocyclyl radical selected from the group consisting of oxiranyl, aziranyl, aziridinyl, 1,2-oxathiolanyl, thienyl, furyl, tetrahydrofuryl, pyranal, thiopyranal, thianthrenyl, isobenzofuranyl, benzofuranyl, chromenyl, 2H-pyrrolyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolidinyl, benzimidazolyl, pyrazolyl, pyrazinyl, pyrazolidinyl, thiazolyl, isothiazolyl, dithiazolyl, oxazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, piperidyl, piperazinyl, pyridazinyl, morpholinyl, thiomorpholinyl, (S-oxo or S,S-dioxo)-thiomorpholinyl, indoliziny, isoindolyl, 3H-indolyl, indolyl, benzimidazolyl, cumaryl, indazolyl, triazolyl, tetrazolyl, purinyl, 4H-quinoliziny, isoquinolyl, quinolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, decahydroquinolyl, octahydroisoquinolyl, benzofuranyl, dibenzofuranyl, benzothiophenyl, dibenzothiophenyl, phthalazinyl, naphthyridinyl, quinoxalyl, quinazoliny, quinazoliny, cinnoliny, pteridinyl, carbazolyl, beta-carboliny, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, furazanyl, phenazinyl, phenothiazinyl, phenoxazinyl, chromenyl, isochromanyl and chromanyl, each of these radicals being unsubstituted or substituted by one to two radicals selected from the group consisting of lower alkyl, especially methyl, ethyl, iso-propyl or tert-butyl, lower alkoxy, especially methoxy, and halo, especially bromo or chloro. In the case of R4, unsubstituted or substituted heterocyclyl is preferably not bound via a ring atom other than a ring nitrogen, but preferably via a carbon in order to avoid overlap with the definition of substituted amino.

In unsubstituted or substituted cycloalkyl, cycloalkyl is preferably a saturated mono- or bicyclic hydrocarbon group with 3 to 16, more preferably 3 to 9 ring carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl, and is substituted by one or more, preferably one to three, substituents independently selected from those described for substituted aryl or is (preferably) unsubstituted.

Unsubstituted or substituted amino is either amino ($-\text{NH}_2$) or amino in which one or two hydrogen atoms are replaced by a substituent independently selected from unsubstituted or substituted alkyl, especially as described below, unsubstituted or substituted aryl, especially as described above, unsubstituted or substituted heterocyclyl, especially as described above, unsubstituted or substituted cycloalkyl, especially as described above, and/or acyl, especially as described below (where preferably only one of the hydrogen atoms is replaced by acyl, the other is hydrogen or a moiety from those just mentioned other than acyl), or substituted amino in the form of an unsubstituted or substituted heterocyclyl as defined above with at least one nitrogen ring atom which is bound via a (preferably not charged, that is including the binding bond tertiary) ring nitrogen atom to the rest of the molecule (thus the substituted amino is one the substituents of which together with the amino nitrogen form a corresponding (unsubstituted or further substituted) heterocyclyl ring), especially selected from the group consisting of aziridinyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolidinyl, benzimidazolyl, pyrazolyl, pyrazinyl, pyrazolidinyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, (S-oxo or S,S-dioxo)-thiomorpholinyl, isoindolyl, indolyl, benzimidazolyl, triazolyl, tetrazolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, decahydroquinolyl, octahydroisoquinolyl, preferably a monocyclic saturated heterocyclyl with at least one nitrogen atom from those just mentioned; where heterocyclyl

is unsubstituted or substituted by one or more, preferably one or to two radicals independently selected from those mentioned as substituents for aryl, preferably from the group consisting of lower alkyl, especially methyl or tert-butyl, lower alkoxy, especially methoxy, and halo, especially bromo or chloro. Especially preferred as unsubstituted or substituted amino are amino, N-mono- or N,N-di-[lower alkyl, N-mono- or N,N-di-(lower alkyl, phenyl and/or phenyl-lower alkyl)-amino-lower alkyl, (unsubstituted or lower alkyl-substituted)-piperidinyl, phenyl and/or phenyl-lower alkyl]-amino, such as N,N-dimethylamino, N,N-diethylamino, 3-[N—(N,N-dimethylamino)-propylamino, 2-[N—(N,N-dimethylamino)-ethylamino or N—(N,N-dimethylamino)-methylamino, N—[(N-mono- or N,N-di-(C₁-C₇-alkyl)-amino)-C₁-C₇-alkyl]-N-(unsubstituted or C₁-C₇-alkyl)-amino, such as N-3-[N—(N,N-dimethylamino)-propyl-N-methyl-amino, N-2-[N—(N,N-dimethylamino)-ethyl-N-methyl-amino or N—(N,N-dimethylamino)-methyl-N-methyl-amino, N-piperidinylamino or N-lower alkyl-N-piperidinylamino wherein piperidinyl is unsubstituted or substituted by lower alkyl, e.g. N-lower alkyl-N-(1-lower alkyl-piperidin-4-yl)-amino, pyrrolidino, piperidino, piperazino, 4-lower alkylpiperazino, such as 4-(methyl, ethyl or isopropyl)-piperazino, morpholino or thiomorpholino.

Unsubstituted or substituted alkyl is preferably C₁- to C₂₀-alkyl, more preferably lower alkyl, that can be linear or branched one or more times (provided the number of carbon atoms allows this) and that is unsubstituted or substituted by one or more, preferably up to three, substituents independently selected from the group consisting of unsubstituted or substituted heterocyclyl as described above, unsubstituted or substituted cycloalkyl as described above, unsubstituted or substituted aryl as defined above, especially phenyl or naphthyl; of lower alkenyl, lower alkynyl, lower alkanoyl, such as acetyl; hydroxy, lower alkoxy, lower-alkoxy-lower alkoxy, (lower-alkoxy)-lower alkoxy-lower alkoxy, phenoxy, naphthyloxy, phenyl- or naphthyl-lower alkoxy, such as benzyloxy; amino-lower alkoxy, lower-alkanoyloxy, benzoyloxy, naphthoyloxy, nitro, halo, cyano, carboxy, lower alkoxy carbonyl, e.g. methoxy carbonyl, n-propoxy carbonyl, iso-propoxy carbonyl or tert-butoxycarbonyl; phenyl- or naphthyl-lower alkoxy carbonyl, such as benzyloxycarbonyl; lower alkanoyl, benzoyl, naphthoyl, carbamoyl, N-mono- or N,N-disubstituted carbamoyl, such as N-mono- or N,N-di-substituted carbamoyl wherein the substituents are selected from lower alkyl and hydroxy-lower alkyl; amidino, guanidino, ureido, mercapto, lower alkylthio, phenyl- or naphthylthio, phenyl- or naphthyl-lower alkylthio, lower alkyl-phenylthio, lower alkyl-naphthylthio, halogen-lower alkylmercapto, lower alkylsulfanyl, phenyl- or naphthyl-sulfanyl, phenyl- or naphthyl-lower alkylsulfanyl, lower alkyl-phenylsulfanyl, lower alkyl-naphthylsulfanyl, sulfo, lower alkanesulfonyl, phenyl- or naphthyl-sulfonyl, phenyl- or naphthyl-lower alkyl-sulfonyl, alkylphenylsulfanyl, halogen-lower alkylsulfanyl, such as trifluoromethanesulfonyl; sulfonamido, benzosulfonamido, amino, N-mono- or N,N-di-[lower alkyl, piperidinyl, N-lower alkylpiperidinyl wherein piperidinyl is unsubstituted or substituted by lower alkyl, N-mono- or N,N-di-(lower alkyl, phenyl and/or phenyl-lower alkyl)-amino]-lower alkyl, phenyl and/or phenyl-lower alkyl)-amino, such as N,N-dimethylamino, N,N-diethylamino, 3-[N—(N,N-dimethylamino)-propylamino, 2-[N—(N,N-dimethylamino)-ethylamino or N—(N,N-dimethylamino)-methylamino, pyrrolidino, piperidino, unsubstituted or N-lower alkyl substituted piperidinyl bound via a ring carbon atom, such as 1-isopropyl-piperidin-4-yl, piperazino, 4-lower alkylpiperazino, such as 4-(methyl, ethyl or isopropyl)-piper-

azino, morpholino or thiomorpholino; where each phenyl or naphthyl (also in phenoxy or naphthoxy) mentioned above as substituent or part of a substituent of substituted alkyl is itself unsubstituted or substituted by one or more, e.g. up to three, preferably 1 or 2, substituents independently selected from halo, especially fluoro, chloro, bromo or iodo, halo-lower alkyl, such as trifluoromethyl, hydroxy, lower alkoxy, amino, N-mono- or N,N-di-(lower alkyl, phenyl, naphthyl, phenyl-lower alkyl and/or naphthyl-lower alkyl)-amino, nitro, carboxy, lower-alkoxycarbonyl carbamoyl, cyano and/or sulfamoyl. Especially preferred are lower alkyl, halo-lower alkyl, such as trifluoromethyl, amino-lower alkyl, such as 3-amino-propyl, 2-aminoethyl or 2-aminomethyl, N-mono- or N,N-di-(lower alkyl, piperidiny, N-lower alkylpiperidiny, phenyl and/or phenyl-lower alkyl)-amino-lower alkyl, such as 3-(N,N-dimethylamino)-propyl, 2-(N,N-dimethylamino)-ethyl, N,N-dimethylaminomethyl, N,N-diethylaminomethyl or N-methyl-N-piperidin-4-yl-amino-methyl, pyrrolidino-lower alkyl, piperidino-lower alkyl, 1-lower alkylpiperidin-4-yl-lower alkyl, piperazino-lower alkyl, such as piperazino-methyl, 4-lower alkylpiperazino-lower alkyl, such as 4-(methyl, ethyl or isopropyl)-piperazino-methyl, or (morpholino or thiomorpholino)-lower alkyl.

Acyl is preferably an organic moiety selected from unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocyclyl or unsubstituted or substituted cycloalkyl, each preferably as described above, bound via a carbonyl (—C(=O)—) or sulfonyl ($\text{—S(=O)}_2\text{—}$) group to the rest of the molecule, that is, a moiety derived from an organic carboxylic or sulfonic acid. Preferred are alkanoyl, especially lower alkanoyl, e.g. acetyl, benzoyl (=phenylcarbonyl), naphthoyl (=naphthylcarbonyl), phenyl- $\text{C}_1\text{—C}_7\text{-alkylcarbonyl}$, naphthyl- $\text{C}_1\text{—C}_7\text{-alkylcarbonyl}$, phenylsulfonyl or lower alkanesulfonyl, where each lower alkanoyl as acyl or each phenyl or naphthyl mentioned as part of acyl are unsubstituted or substituted by one or more, e.g. up to three, preferably 1 or 2, substituents independently selected from halo, especially fluoro, chloro, bromo or iodo, halo-lower alkyl, such as trifluoromethyl, hydroxy, lower alkoxy, amino, N-mono- or N,N-di-(lower alkyl, phenyl, naphthyl, phenyl-lower alkyl or naphthyl-lower alkyl)amino, nitro, carboxy, lower-alkoxycarbonyl, carbamoyl, cyano and/or sulfamoyl. Preferred are lower alkanoyl, benzoyl, phenylsulfonyl or tolylsulfonyl.

In unsubstituted or substituted alkenyl, alkenyl has one or more double bonds and preferably has 2 to 20, more preferably up to 12, carbon atoms; it is linear or can be branched one or more times (provided the number of carbon atoms allows this). Preferred is $\text{C}_2\text{—C}_7\text{-alkenyl}$, especially C_3 or $\text{C}_4\text{-alkenyl}$, such as allyl or crotyl. Alkenyl can be unsubstituted or substituted, especially by one or more, more especially up to three, of the substituents mentioned above as substituents for substituted alkyl, with the proviso that N, S or O with an active hydrogen is preferably not bound at a carbon atom from which a double bond emerges (as this would lead to tautomerism). Also other substituents that are not sufficiently stable are preferably excluded. Unsubstituted alkenyl, in particular $\text{C}_2\text{—C}_7\text{-alkenyl}$, is preferred. Unsubstituted or substituted alkynyl is preferably a moiety with one or more triple bonds and preferably has 2 to 20, more preferably up to 12, carbon atoms; it is linear or can be branched one or more times (provided the number of carbon atoms allows this). Preferred is $\text{C}_2\text{—C}_7\text{-alkynyl}$, especially C_3 or $\text{C}_4\text{-alkynyl}$, such as ethynyl or propyn-2-yl. Alkynyl can be unsubstituted or substituted, especially by one or more, more especially up to three, of the substituents mentioned above for substituted alkyl. Substituents such as amino or hydroxy (with free dissociable hydro-

gen) preferably are not bound to carbon atoms that participate at a triple bond, and also other substituents that are not sufficiently stable are preferably excluded. Unsubstituted alkynyl, in particular $\text{C}_2\text{—C}_7\text{-alkynyl}$, or N,N-di-(lower alkyl, phenyl and/or phenyl lower alkyl)- $\text{C}_3\text{—C}_7\text{-alkynyl}$, such as 3-(N,N-dimethylamino)-prop-1-ynyl, is preferred.

The terms “treatment” or “therapy” (especially of tyrosine protein kinase dependent diseases or disorders) refer to the prophylactic (including preventative, e.g. in patients where mutations or changes have been found that indicate that they are or may be prone to the development of a disease) or preferably therapeutic (including but not limited to palliative, curative, symptom-alleviating, symptom-reducing, disease- or symptom-suppressing, progression-delaying, kinase-regulating and/or kinase-inhibiting) treatment of said diseases, especially of any one or more of the diseases mentioned below.

The term “curative” means efficacy in treating ongoing episodes involving (specially deregulated) receptor tyrosine kinase activity.

The term “prophylactic” means the prevention of the onset or recurrence of diseases involving deregulated receptor tyrosine kinase activity.

The term “delay of progression” as used herein especially means administration of the active compound to patients being in a pre-stage or in an early phase of the disease to be treated, in which patients for example a pre-form of the corresponding disease is diagnosed or which patients are in a condition, e.g. during a medical treatment or a condition resulting from an accident, under which it is likely that a corresponding disease will develop, or where e.g. metastasation can be expected without treatment.

An animal is preferably a warm-blooded animal (or patient), more preferably a mammal, especially a human.

Where subsequently or above the term “use” is mentioned (as verb or noun) (relating to the use of a compound of the formula I or a pharmaceutically acceptable salt thereof), this (if not indicated differently or suggested differently by the context) includes any one or more of the following embodiments of the invention, respectively (if not stated otherwise): the use in the treatment of a protein (especially tyrosine) kinase dependent disease, the use for the manufacture of pharmaceutical compositions for use in the treatment of a protein kinase dependent disease, methods of use of one or more compounds of the present invention in the treatment of a protein kinase dependent and/or proliferative disease, pharmaceutical preparations comprising one or more compounds of the formula I for the treatment of said protein kinase dependent disease, and one or more compounds of the formula I in the treatment of said protein kinase dependent disease, as appropriate and expedient, if not stated otherwise. In particular, diseases to be treated and are thus preferred for “use” of a compound of formula I are selected from (especially tyrosine) protein kinase dependent (“dependent” meaning also “supported”, not only “solely dependent”, including also situations where a disease is responding to modulation, especially inhibition, of a protein kinase) diseases mentioned below, especially proliferative diseases mentioned below.

Where a protein kinase is mentioned, this relates to any type of protein kinase, especially serine/threonine and/or preferably protein tyrosine kinases, most preferably one or more tyrosine kinases selected from the group consisting of tie-2 and/or more especially PDGFR, VEGFR-2, c-Abl, Flt3, Ret, kit and IGF1-R including one or more altered or mutated or allelic forms of any one or more of these (e.g. those that result in conversion of the respective proto-oncogene into an oncogene, such as constitutively activated mutants, e.g. Bcr-

Abl). Especially an abnormally highly-expressed, constitutively activated or normal but in the given context of other regulatory mechanism in a patient relatively overactive, and/or mutated form is encompassed.

In another aspect the present invention provides a compound of the present invention in the form of a salt.

Salts are especially the pharmaceutically acceptable salts of compounds of formula I. They can be formed where salt forming groups, such as basic or acidic groups, are present that can exist in dissociated form at least partially, e.g. in a pH range from 4 to 10 in aqueous environment, or can be isolated especially in solid form.

A salt includes pharmaceutically acceptable and pharmaceutically non-acceptable salts of a compound of formula I, e.g. for preparation/isolation/purification purposes; preferably a pharmaceutically acceptable salt. For pharmaceutical use pharmaceutically non-acceptable salts of a compound of the present invention are excluded.

Salts can be formed where salt forming groups, such as basic or acidic groups, are present that can exist in dissociated form at least partially, e.g. in a pH range from 4 to 10 in aqueous environment, or can be isolated, e.g. in solid form.

Such salts may be formed, for example, as acid addition salts, preferably with organic or inorganic acids, from compounds of formula I with a basic nitrogen atom, especially the pharmaceutically acceptable salts. Suitable inorganic acids are, for example, halogen acids, such as hydrochloric acid, sulfuric acid, or phosphoric acid. Suitable organic acids are, for example, carboxylic, phosphonic, sulfonic or sulfamic acids, for example acetic acid, propionic acid, lactic acid, fumaric acid, succinic acid, citric acid, amino acids, such as glutamic acid or aspartic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, benzoic acid, methane- or ethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 1,5-naphthalene-disulfonic acid, N-cyclohexylsulfamic acid, N-methyl-, N-ethyl- or N-propyl-sulfamic acid, or other organic protonic acids, such as ascorbic acid.

In the presence of negatively charged radicals, such as carboxy or sulfo, salts may also be formed with bases, e.g. metal or ammonium salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium, magnesium or calcium salts, or ammonium salts with ammonia or suitable organic amines, such as tertiary monoamines, for example triethylamine or tri(2-hydroxyethyl)amine, or heterocyclic bases, for example N-ethyl-piperidine or N,N'-dimethylpiperazine.

When a basic group and an acid group are present in the same molecule, a compound of formula I may also form internal salts.

For preparation, isolation or purification purposes it is also possible to use pharmaceutically unacceptable salts, for example picrates or perchlorates. For therapeutic use, only pharmaceutically acceptable salts or free compounds are employed (where applicable comprised in pharmaceutical preparations), and these are therefore preferred.

In view of the close relationship between the compounds in free form and in the form of their salts, including those salts that can be used as intermediates, for example in the purification or identification of the compounds or salts thereof, any reference to "compounds" (including also starting materials and "intermediates") hereinbefore and hereinafter, especially to the compound(s) of the formula I, is to be understood as referring also to one or more salts thereof or a mixture of a free compound and one or more salts thereof, each of which is intended to include also any solvate, metabolic precursor such as ester or amide of the compound of formula I, or salt of

any one or more of these, as appropriate and expedient and if not explicitly mentioned otherwise. Different crystal forms and solvates may be obtainable and then are also included.

Where the plural form is used for compounds, salts, pharmaceutical preparations, diseases, disorders and the like, this is intended to mean also a single compound, salt, pharmaceutical preparation, disease or the like, where "a" or "an" is used, this means to refer to the indefinite article, or preferably to "one".

A compound of the present invention in free form may be converted into a corresponding compound in the form of a salt; and vice versa. A compound of the present invention in free form or in the form of a salt and in the form of a solvate may be converted into a corresponding compound in free form or in the form of a salt in non-solvated form; and vice versa.

A compound of the present invention may exist in the form of isomers and mixtures thereof; e.g. optical isomers, diastereoisomers, cis/trans conformers. A compound of the present invention may e.g. contain asymmetric carbon atoms and may thus exist in the form of enantiomers or diastereoisomers and mixtures thereof, e.g. racemates. A compound of the present invention may be present in the (R)-, (S)- or (R,S)-configuration preferably in the (R)- or (S)-configuration regarding each of the substituents at such asymmetric carbon atoms in a compound of the present invention.

Isomeric mixtures may be separated as appropriate, e.g. according, e.g. analogously, to a method as conventional, to obtain pure isomers. The present invention includes a compound of the present invention in any isomeric form and in any isomeric mixture.

E.g. in some cases, a compound of the present invention may comprise one or more chiral centers in substituents or show other asymmetry (leading to enantiomers) or may otherwise be able to exist in the form of more than one stereoisomer, e.g. due more than one chiral centers or more than one other type of asymmetry or due to rings or double bonds that allow for Z/E (or cis-trans) isomerism (diastereomers). The present inventions includes both, mixtures of two or more such isomers, such as mixtures of enantiomers, especially racemates, as well as preferably purified isomers, especially purified enantiomers or enantiomerically enriched mixtures.

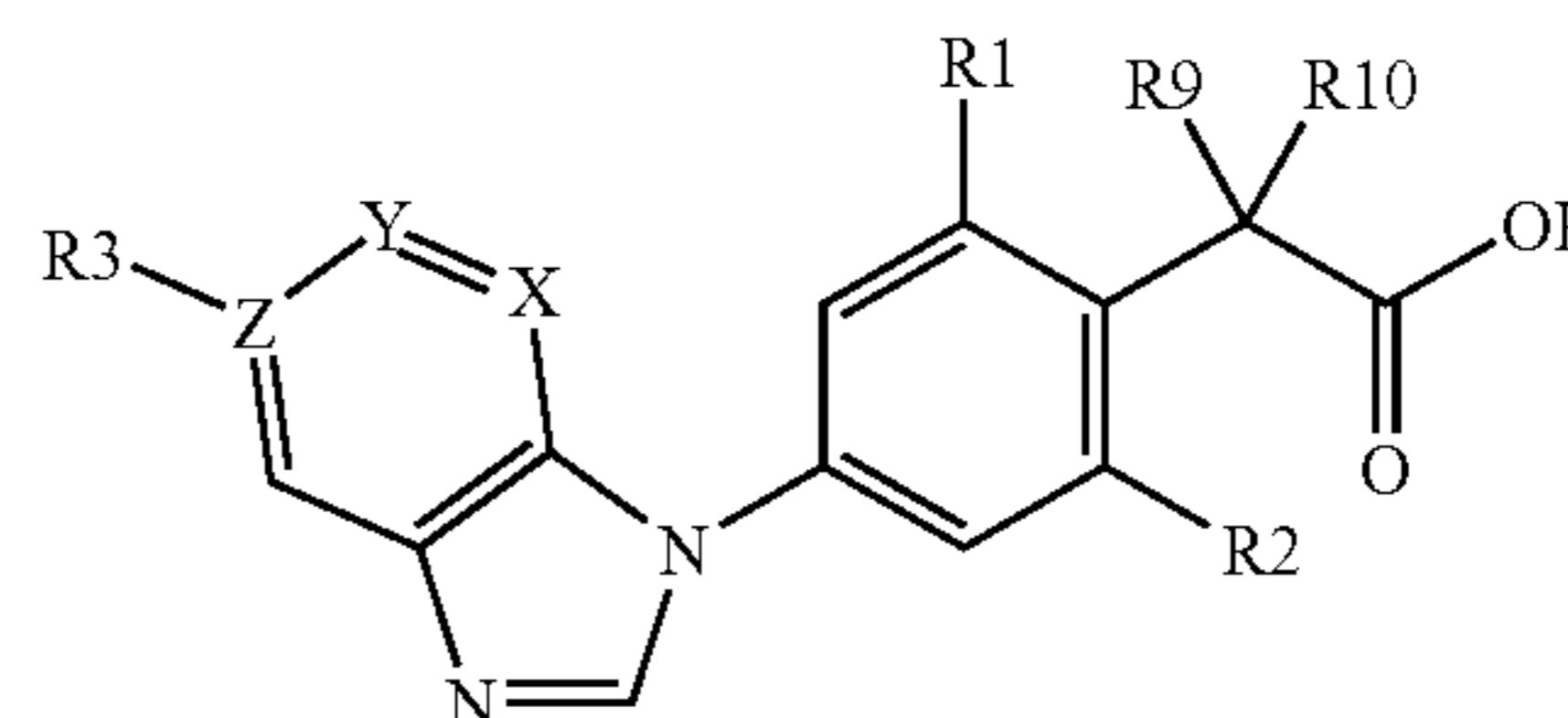
The present invention also includes tautomers of a compound of the present invention, where tautomers can exist.

Production Processes

Each compound described herein may be prepared as appropriate, e.g. as described herein, or according, e.g. analogously, to a method as conventional. A compound of formula I may be prepared analogously to methods that, for other compounds, are in principle known in the art, so that for the novel compounds of the formula I the process is novel as analogy process.

In another aspect the present invention provides a process for the production of a compound of formula I, wherein the residues are as defined above, comprising the steps

i) reacting a carboxylic acid compound of formula,



17

or a reactive derivative thereof, wherein R1, R2, R3, R9, R10, X, Y and Z are as defined for a compound of the formula I, with an amino compound of formula



wherein Q is as defined for a compound of formula I, and ii) isolating a compound of formula I obtained from the reaction mixture;

e.g. and, optionally,

transforming an obtainable compound of formula I into a different compound of formula I,

transforming a salt of an obtainable compound of formula I into the free compound or a different salt,

transforming an obtainable free compound of formula I into a salt thereof, and/or -separating an obtainable mixture of isomers of a compound of formula I into individual isomers;

where in any one or both starting materials of the formula II and/or III functional groups that shall not take part in the reaction may be present in protected form and protecting groups are removed to obtain a compound of the formula I.

The condensation of an acid of the formula II, or a reactive derivative thereof, under () preferably takes place under customary condensation conditions, where among the possible reactive derivatives of an acid of the formula II reactive esters (such as the hydroxybenzotriazole (HOBT), pentafluorophenyl, 4-nitrophenyl or N-hydroxysuccinimide ester), acid halogenides (such as the acid chloride or bromide) or reactive anhydrides (such as mixed anhydrides with lower alkanolic acids or symmetric anhydrides) are preferred. Reactive carbonic acid derivatives can also and preferably be formed in situ. The reaction can then be carried out by dissolving the compounds of formulae II and III in a suitable solvent, for example a halogenated hydrocarbon, such as methylene chloride, N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidone, methylene chloride, or a mixture of two or more such solvents, and by the addition of a suitable base, for example triethylamine, diisopropylethylamine (DIEA) or N-methylmorpholine and, if the reactive derivative of the acid of the formula II is formed in situ, a suitable coupling agent that forms a preferred reactive derivative of the carbonic acid of formula III in situ, for example dicyclohexylcarbodiimide/1-hydroxybenzotriazole (DCC/HOBT); bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl); O-(1,2-dihydro-2-oxo-1-pyridyl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TPTU); O-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU); (benzotriazol-1-yloxy)-tripyrrolidinophosphonium-hexafluorophosphate (PyBOP), 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride/hydroxybenzotriazole or/1-hydroxy-7-azabenzotriazole (EDC/HOBT or EDC/HOAt) or HOAt alone, or with (1-chloro-2-methyl-propenyl)-dimethylamine. For review of some other possible coupling agents, see e.g. Klauser; Bodansky, *Synthesis* 1972, 453-463. The reaction mixture is preferably stirred at a temperature of from approximately -20 to 50° C., especially from -5° C. to 30° C., e.g. at 0° C. to room temperature. The reaction may preferably be carried out under an inert gas, e.g. nitrogen or argon. If required, the subsequent removal of protecting groups takes place. The subsequent removal of a protecting group, such as tert-butoxycarbonyl, methoxymethyl, benzyl, 2-(trimethylsilyl)-ethoxycarbonyl or tert-butyl dimethylsilyl, if required, takes place under standard conditions, see also the literature mentioned below under General Process Conditions.

18

Optional Reactions and Conversions

Compounds of the formula I, or protected forms thereof directly obtained according to the preceding procedure or after introducing protecting groups anew, which are included subsequently as starting materials for conversions as well even if not mentioned specifically, can be converted into different compounds of the formula I according to known procedures, where required followed removal of protecting groups.

For example, in a compound of the formula I wherein Q is aryl that is substituted by iodo or bromo and possibly one or more other substituents, such as trifluoro, e.g. where Q is 4-iodo-3-trifluoromethylphenyl, the bromo or iodo may be replaced with substituted or unsubstituted phenyl, such as 4-cyanophenyl, by coupling reaction with the corresponding substituted or unsubstituted phenylboronic acid of formula,



wherein Phe is unsubstituted or substituted aryl, in the presence of a catalyst, especially PdCl₂(dppf) and preferably also a base, such as an alkali metal carbonate, e.g. sodium carbonate, in an appropriate solvent or solvent mixture, e.g. toluene/water, at, for example, elevated temperatures, e.g. between 30° C. and the (preferred) reflux temperature.

Salts of compounds of formula I having at least one salt-forming group may be prepared in a manner known per se. For example, salts of compounds of formula I having acid groups may be formed, for example, by treating the compounds with metal compounds, such as alkali metal salts of suitable organic carboxylic acids, e.g. the sodium salt of 2-ethylhexanoic acid, with organic alkali metal or alkaline earth metal compounds, such as the corresponding hydroxides, carbonates or hydrogen carbonates, such as sodium or potassium hydroxide, carbonate or hydrogen carbonate, with corresponding calcium compounds or with ammonia or a suitable organic amine, stoichiometric amounts or only a small excess of the salt-forming agent preferably being used. Acid addition salts of compounds of formula I are obtained in customary manner, e.g. by treating the compounds with an acid or a suitable anion exchange reagent. Internal salts of compounds of formula I containing acid and basic salt-forming groups, e.g. a free carboxy group and a free amino group, may be formed, e.g. by the neutralisation of salts, such as acid addition salts, to the isoelectric point, e.g. with weak bases, or by treatment with ion exchangers.

A salt of a compound of the formula I can be converted in customary manner into the free compound; metal and ammonium salts can be converted, for example, by treatment with suitable acids, and acid addition salts, for example, by treatment with a suitable basic agent. In both cases, suitable ion exchangers may be used.

Stereoisomeric mixtures, e.g. mixtures of diastereomers, can be separated into their corresponding isomers in a manner known per se by means of appropriate separation methods. Diastereomeric mixtures for example may be separated into their individual diastereomers by means of fractionated crystallization, chromatography, solvent distribution, and similar procedures. This separation may take place either at the level of one of the starting compounds or in a compound of formula I itself. Enantiomers may be separated through the formation of diastereomeric salts, for example by salt formation with an enantiomer-pure chiral acid, or by means of chromatography, for example by HPLC, using chromatographic substrates with chiral ligands.

19

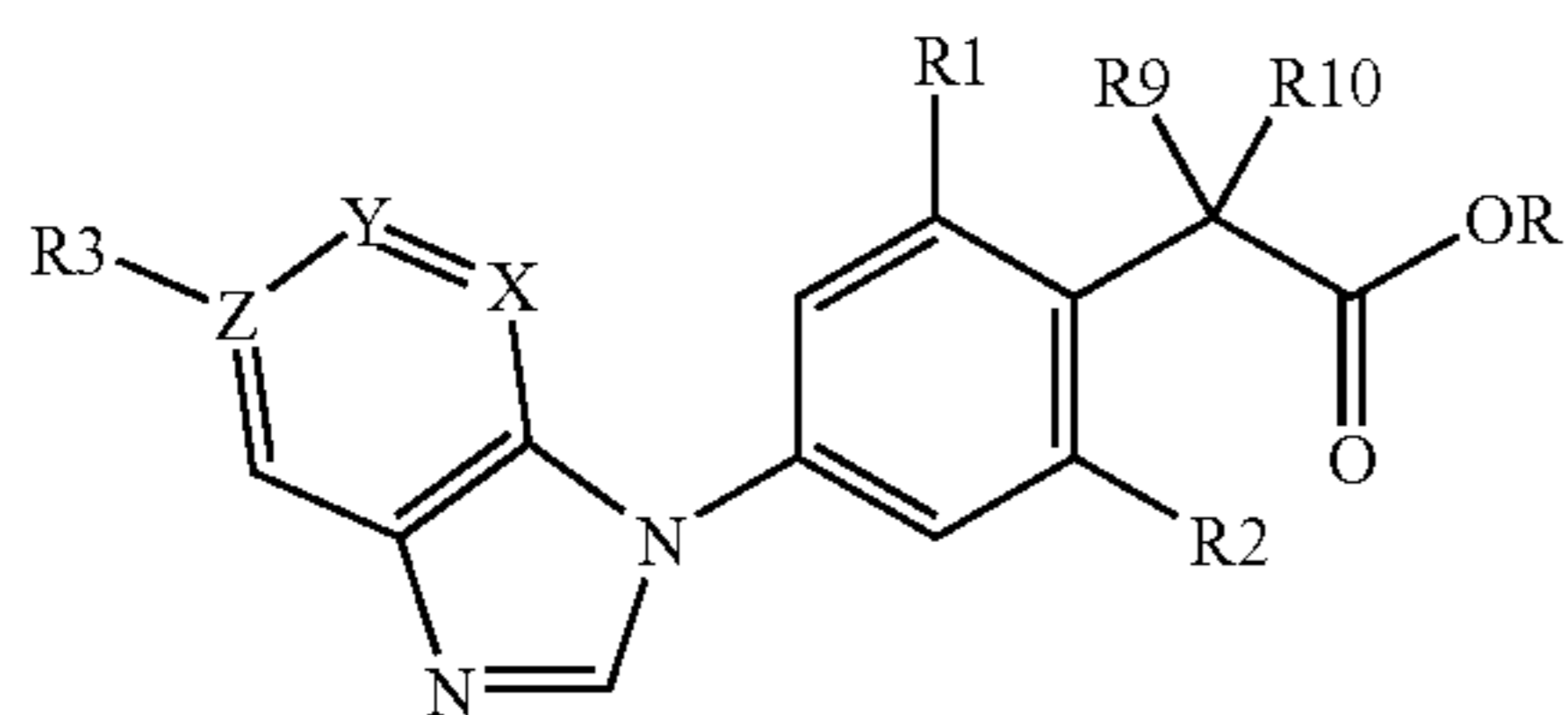
Intermediates and final products can be worked up and/or purified according to standard methods, e.g. using chromatographic methods, distribution methods, (re-) crystallization, and the like.

Starting Materials

Starting Materials, including intermediates, for compounds of the formula I, such as the compounds of the formulae II and III, can be prepared, for example, according to methods that are known in the art, according to methods described in the examples or methods analogous to those described in the examples, and/or they are known or commercially available.

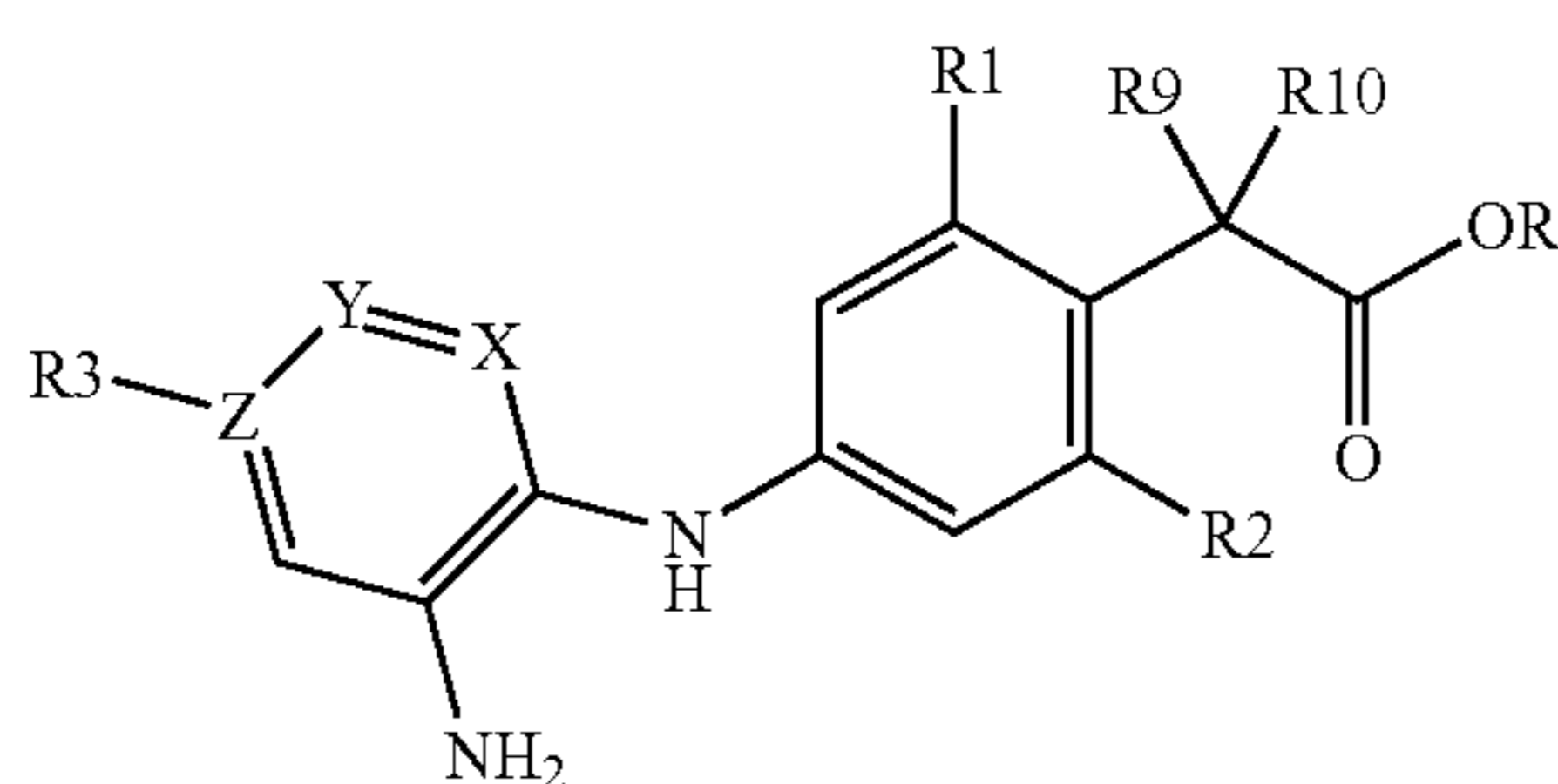
In the subsequent description of starting materials and intermediates and their synthesis, R1, R2, R3, R4, R5, R6, R7, R8, X, Y, Z and Q have the meanings given above or in the Examples for the respective starting materials or intermediates, if not indicated otherwise directly or by the context. Protecting groups, if not specifically mentioned, can be introduced and removed at appropriate steps in order to prevent functional groups, the reaction of which is not desired in the corresponding reaction step or steps, employing protecting groups, methods for their introduction and their removal are as described above or below, e.g. in the references mentioned under "General Process Conditions". The person skilled in the art will readily be able to decide whether and which protecting groups are useful or required.

A starting material of the formula II may be prepared, for example, from a corresponding ester (which, if it is an active ester, may be used directly as a reactive derivative of a compound of the formula II in the process of manufacture of a compound of the formula I) of formula



wherein R is the residue of an alcohol, e.g. alkyl or phenyl-lower alkyl, such as methyl, ethyl or benzyl, by hydrolysis, e.g. in the presence of bases, such as an alkali metal hydroxide, e.g. lithium hydroxide, in an appropriate solvent, such as an ether, e.g. tetrahydrofuran, at customary temperatures, e.g. from 20 to 50° C., or in the presence of acids, such as hydrohalic acids, e.g. hydrochloric acid, in an appropriate solvent, such as water, at customary temperatures, e.g. from 50° C. to the reflux temperature of the reaction mixture.

A compound of formula V may be obtained e.g. by reaction from an amino compound of formula,



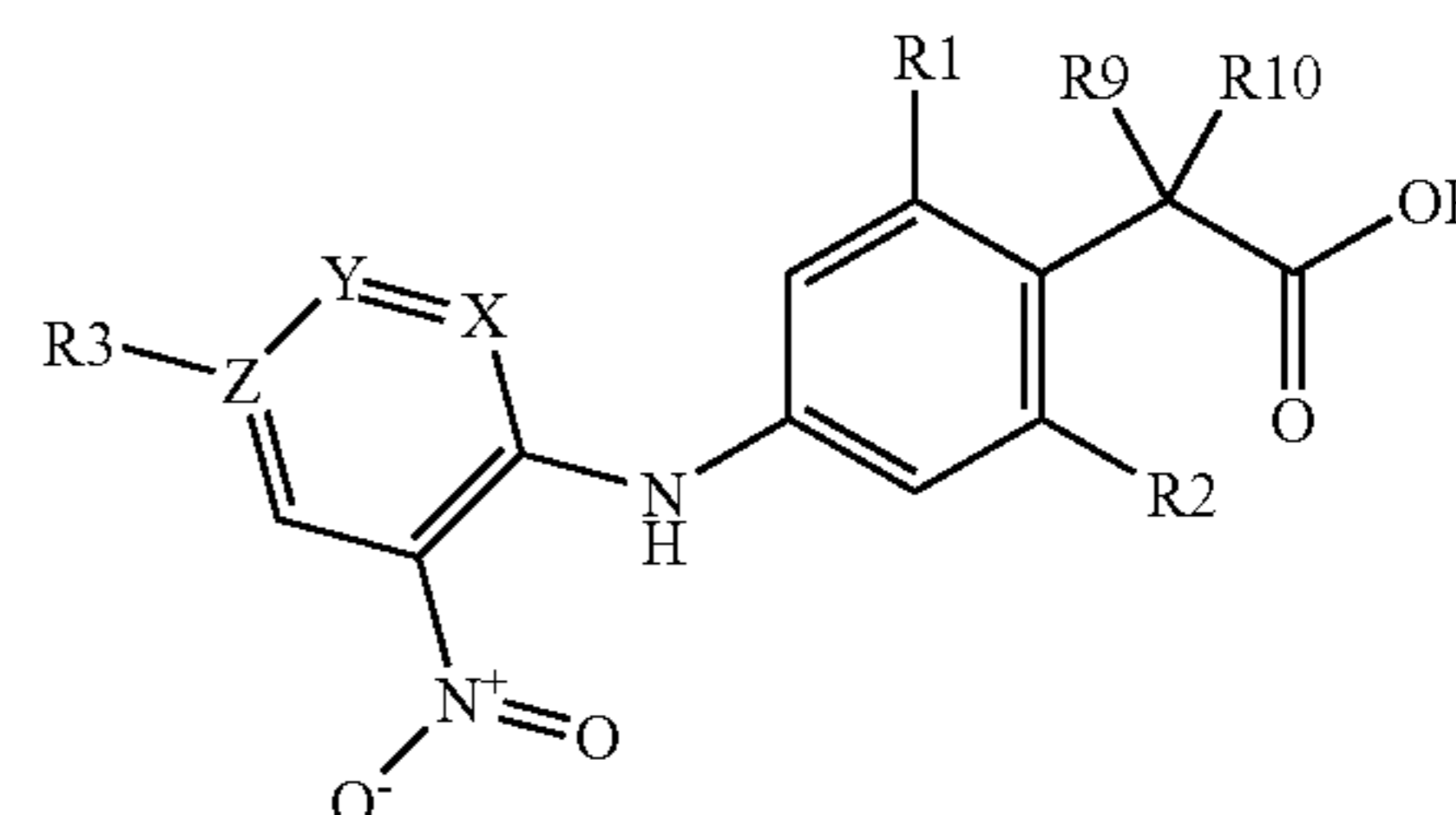
VI

wherein R is as defined for a compound of the formula V, and the other residues are as defined for a compound of formula I, under appropriate conditions e.g., where Z is N and each of Y and X is CH and Hal is chloro or bromo in a compound of formula VIII, at preferably elevated temperatures, e.g. from 30° C. to the reflux temperature of the reaction mixture, in an appropriate solvent, such as an alcohol and/or an ether, e.g. methanol and/or dioxane; in the case where X in a compound of formula VIII is N, Y is CH and Z is C, in the presence or (especially if R2 is halo) absence of an acid, such as hydrochloric acid, in an appropriate solvent, such as an alcohol and/or an ether, e.g. methanol and/or dioxane, preferably at

20

wherein R is as defined for a compound of formula V and wherein the other residues are as defined for a compound of formula I, by reaction with an appropriate form of formic acid, especially tri-lower alkyl orthoformate, such as triethyl orthoformate, preferably at elevated temperatures, e.g. under reflux conditions, and in the presence or preferably the absence of an appropriate solvent.

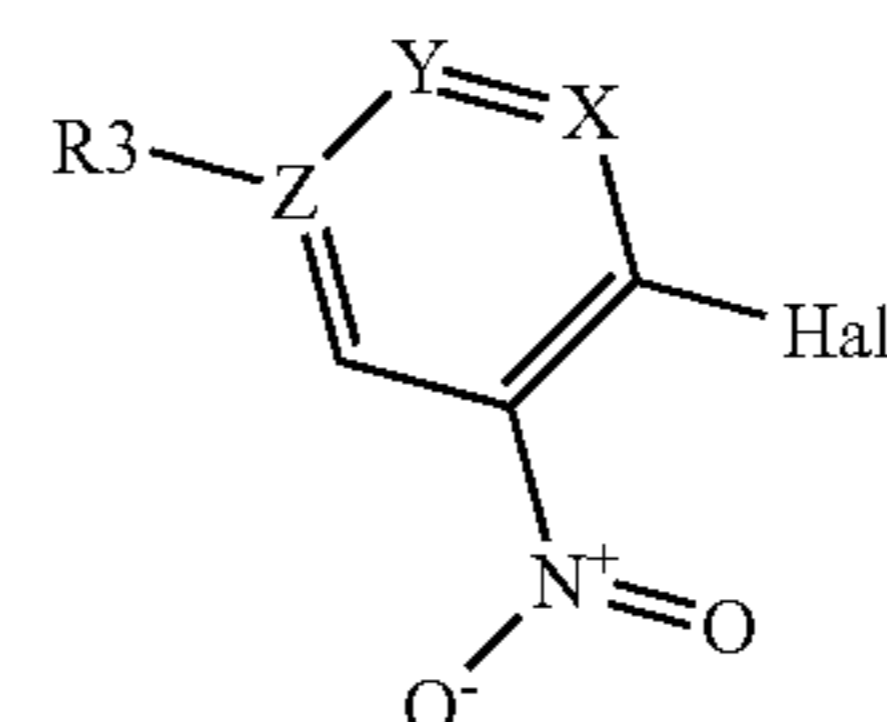
An amino compound of formula VI may be obtained e.g. by reducing a corresponding nitro precursor compound of formula



VII

wherein R is as defined for a compound of formula V and wherein the other residues are as defined for a compound of formula I, preferably by catalytic hydrogenation, e.g. with hydrogen in the presence of a Raney catalyst, such as Raney nickel, in an appropriate solvent, such as an alcohol, e.g. methanol, at customary temperatures, e.g. from 0 to 50° C.

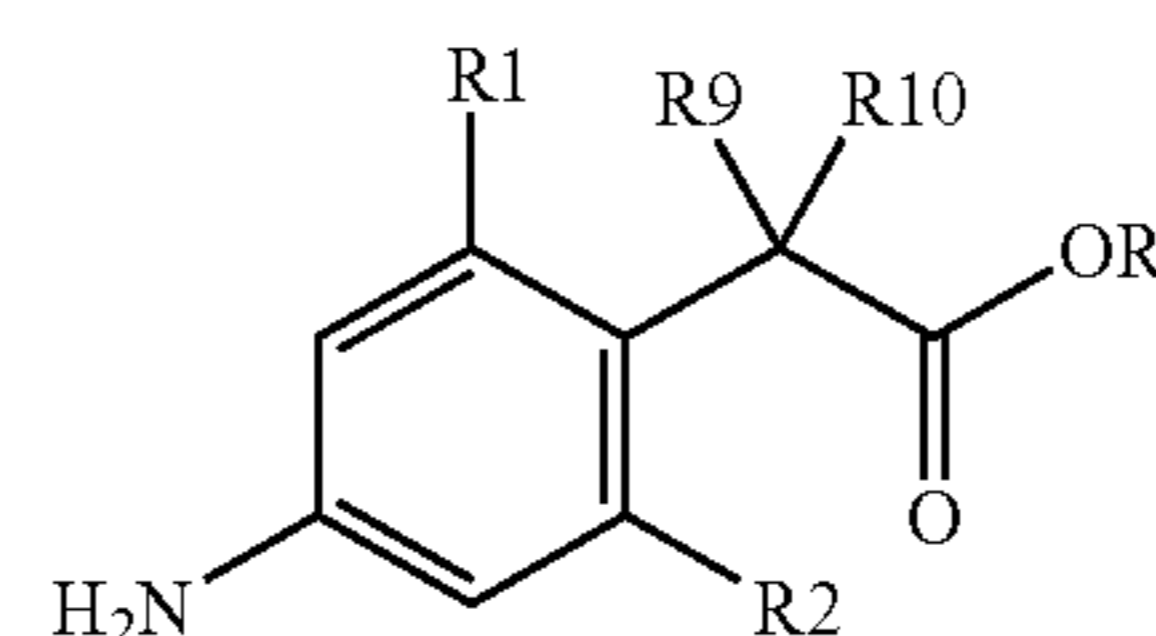
A nitro compound of formula VII may be obtained e.g. by reacting a halo compound of formula,



V

VIII

wherein Hal is halo, especially fluoro, chloro or bromo, and X, Y Z and R3 are as defined for a compound of formula I, under substitution conditions with an amine of formula,



IX

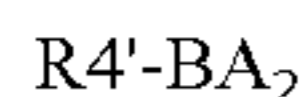
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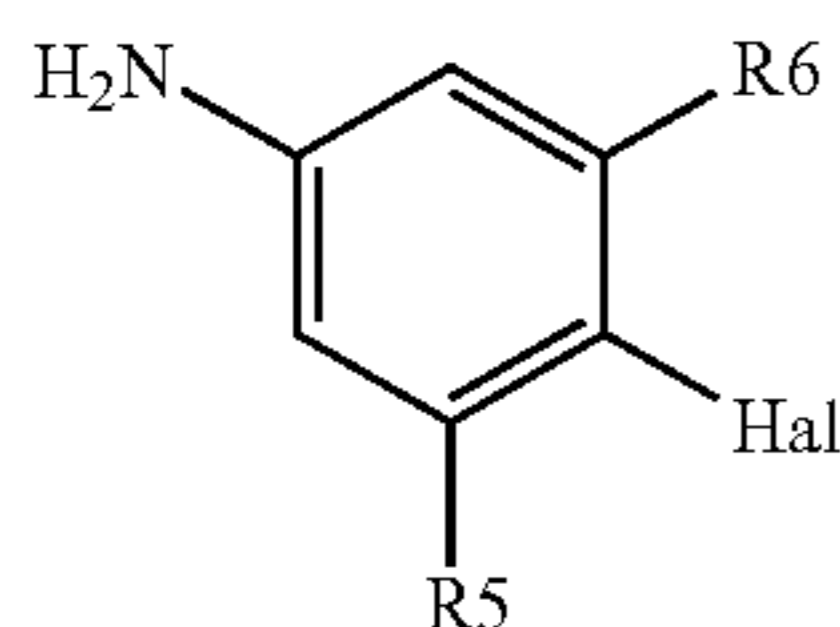
elevated temperatures, e.g. from 30° C. to the reflux temperature of the reaction mixture; or where X and Y are CH and Z is C and Hal is F in a compound of the formula VIII, in the presence or preferably absence of an appropriate solvent at elevated temperatures, e.g. in a sealed tube at 100 to 150° C.; or using appropriate variations of these reaction conditions. A compound of the formula VII may also be prepared as described in WO 97/21665 which, especially regarding this synthesis, is preferably included herein by reference.

Starting materials of formula III may be prepared by or in analogy to methods that are described in the literature, e.g. in WO03099771 or WO0009495 which, especially regarding the manufacture of such starting materials, are preferably incorporated herein by reference.

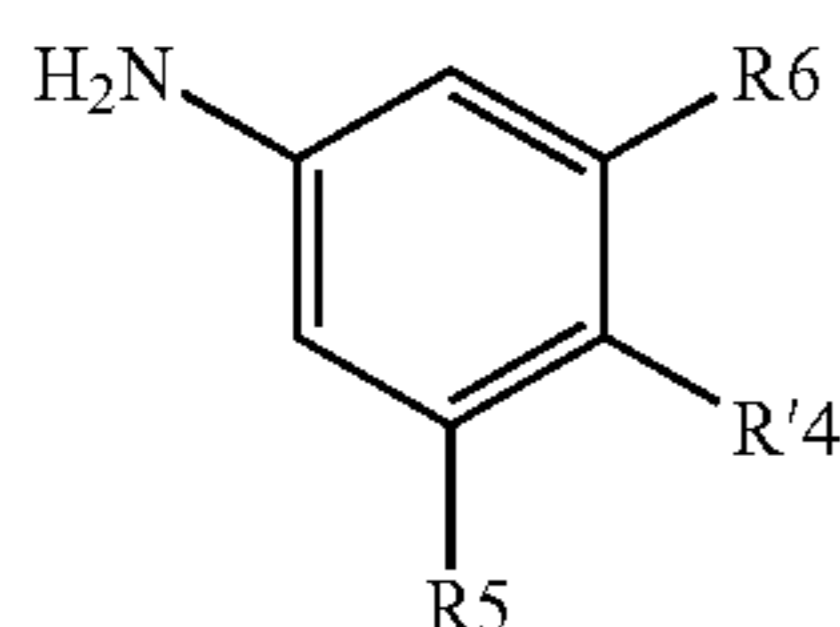
Starting materials of formula III wherein Q is a group of formula A, wherein R'4 is unsubstituted or substituted aryl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl or unsubstituted or substituted alkynyl may be obtained e.g. under common coupling conditions, e.g. under Suzuki coupling conditions. For example, a compound of formula



wherein R'4 is as defined above, especially unsubstituted or substituted aryl, and BA₂ is B(OD)₂ wherein D is hydrogen or lower alkyl, 9-borabicyclo[3.3.1]nonanyl or B(CHCH₃CH(CH₃)₂)₂, may be reacted in the presence of an appropriate catalyst, e.g. Pd(PPh₃)₄ or PdCl₂(dppf), in the presence of a base, e.g. an alkali metal carbonate, such as sodium carbonate, an alkali metal alcoholate, e.g. sodium ethanolate, a hydroxide, such as TIOH, a tertiary amine, such as triethylamine, or an alkali metal phosphate, such as potassium phosphate, in an appropriate solvent, such as toluene and/or water, preferably at elevated temperatures, e.g. under reflux conditions, with a compound of formula



wherein Hal is halo, especially bromo; and the other residues are as defined in a compound of formula I, to obtain a compound of formula

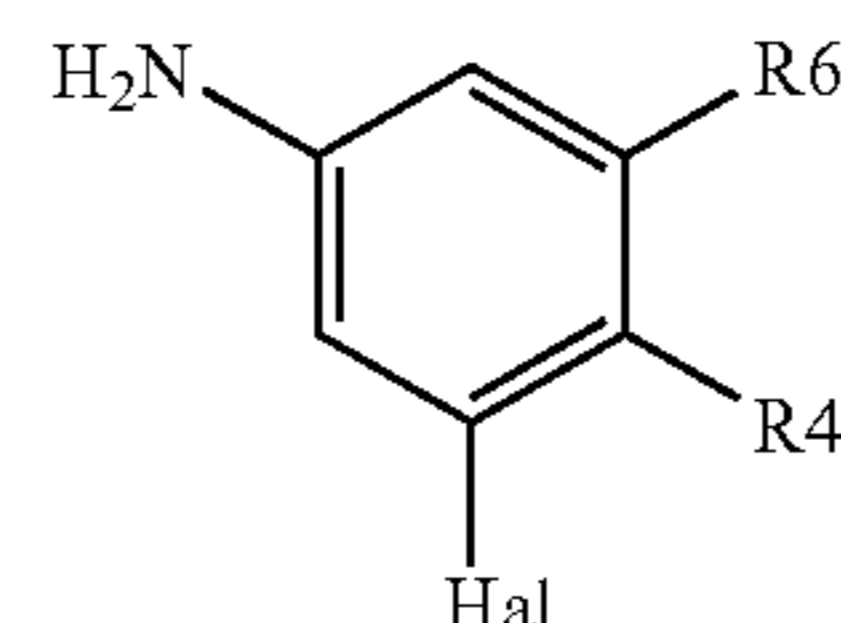


wherein R'4 is as defined above and which is a compound of formula III wherein R'4 has the meaning of R4 as defined in a compound of formula I.

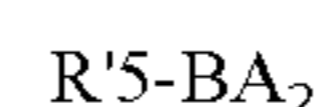
A compound of formula III wherein Q is a group of formula A, wherein R'5 is unsubstituted or substituted aryl or unsubstituted or substituted heterocyclyl, may be obtained e.g. under common coupling conditions, e.g. under Suzuki coupling conditions, e.g. as just described for the reaction of a

22

compound of formula X with a compound of formula XI, e.g. by reaction of a compound of the formula

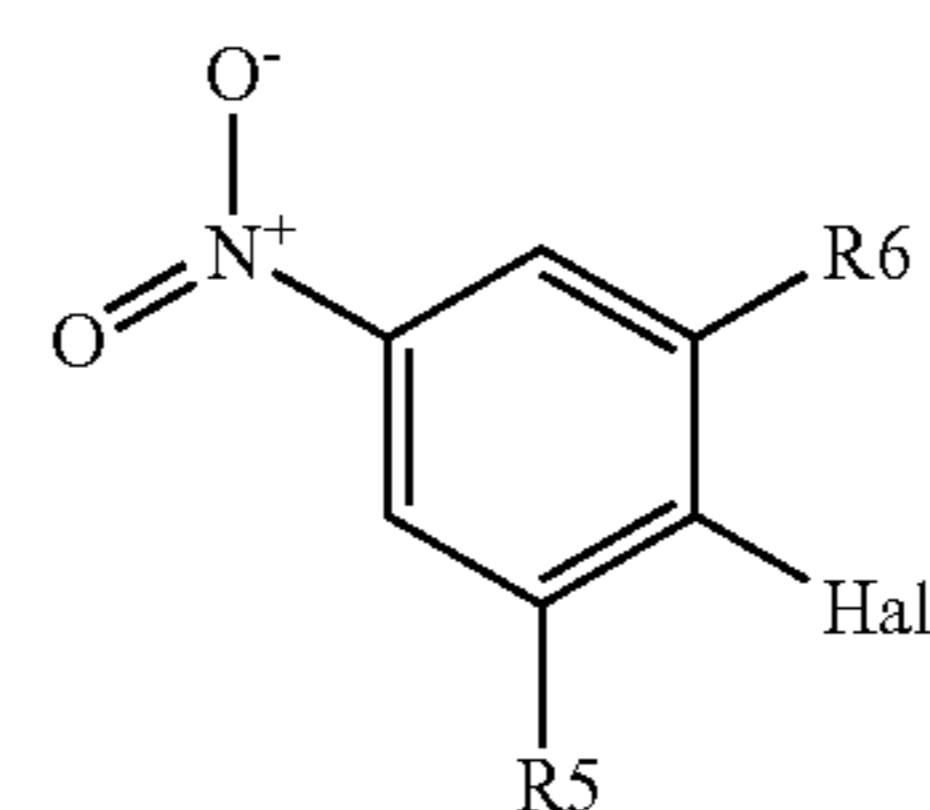


wherein Hal is halo, especially bromo, and R4 and R6 are as defined for a compound of formula I, preferably R4 is hydrogen, with a compound of formula

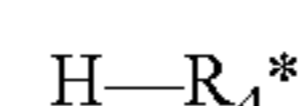


wherein R'5 is as defined above and BA₂ is as defined above for a compound of formula X.

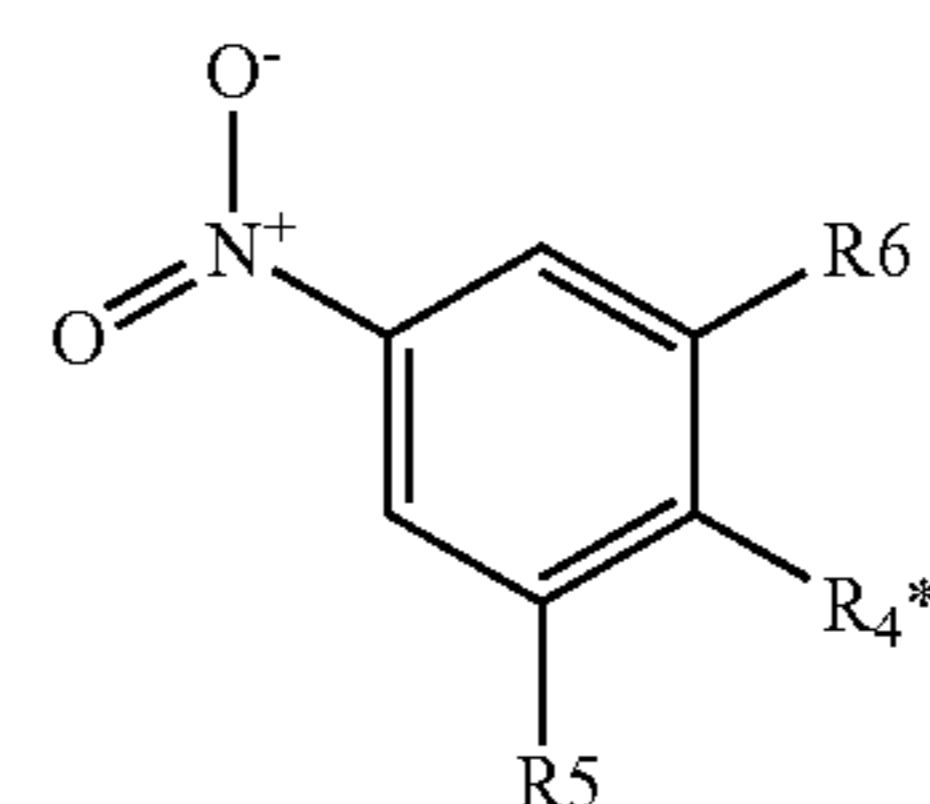
A compound of formula III wherein Q is a moiety of formula A wherein R4 is unsubstituted or substituted amino may be obtained e.g. by reaction of a compound of formula



wherein Hal is halo, especially bromo, and R5 and R6 are as defined for a compound of formula I, with a compound of formula

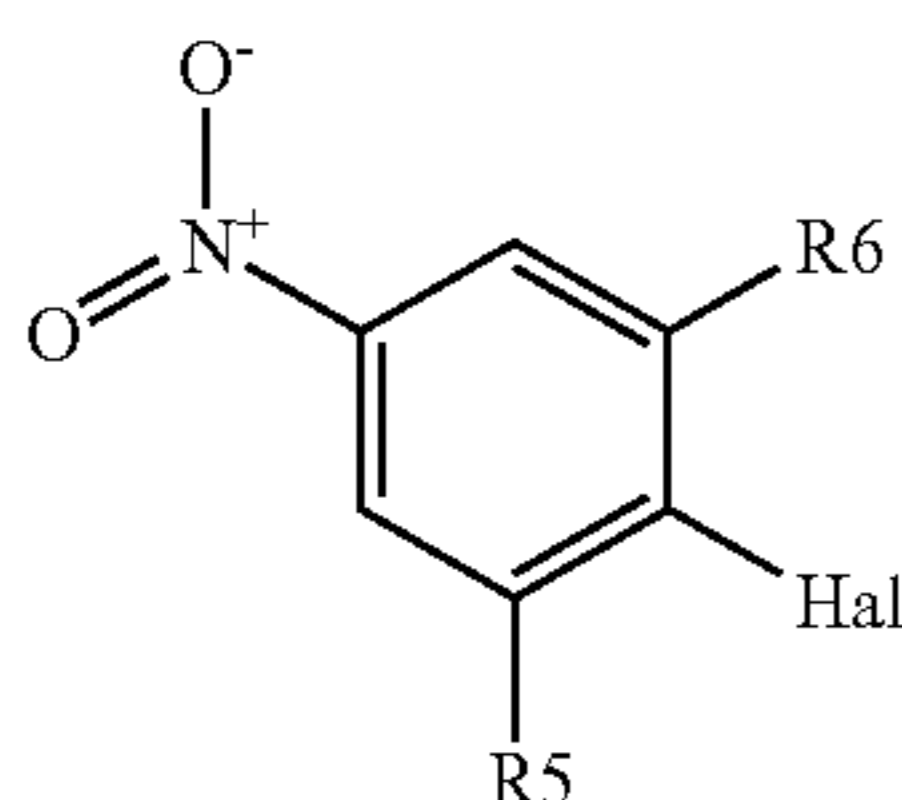


wherein R₄* is unsubstituted or (preferably) substituted amino, in the presence or, preferably absence, of an appropriate solvent, preferably at elevated temperatures, e.g. from 100 to 150° C., e.g. in a sealed tube, to obtain a compound of formula



wherein R₄* is as defined above and R5 and R6 are as defined in a compound of formula I. The nitro group in a compound of formula XVII may be reduced to amino to give a corresponding amino compound of formula III, e.g. by catalytic hydrogenation, for example in the presence of hydrogen and a hydrogenation catalyst, e.g. a Raney catalyst, such as Raney-Ni, or a noble metal catalyst, e.g. palladium, preferably on a carrier, such as charcoal, in an appropriate solvent, e.g. an alcohol, such as methanol or ethanol, at temperatures e.g. from 0 to 50° C.

A compound of formula XI (which also falls under a compound of the formula III) wherein Hal is halo, especially iodo, may be obtained e.g. by reducing the nitro group in a nitro compound of formula



XVIII

wherein Hal is halo, especially iodo, to the amino group, e.g. under conditions as described for the hydrogenation of a compound of formula XVII. A compound of formula XVIII (e.g. wherein R5 is trifluoromethyl, Hal is iodo and R6 is hydrogen) may be obtained e.g. as or in analogy to a method as described in WO 0009495 which is, especially with regard to this synthesis, preferably incorporated herein by reference.

Other starting materials, e.g. those of the formula VIII, IX, X, XI, XIII, XIV, XVI and XVIII, are known, commercially available and/or may be prepared according, e.g. analogously, to a method as conventional, e.g. according, e.g. analogously, to known or standard procedures, or by a method as described herein.

General Process Conditions

The following applies in general to all processes mentioned hereinbefore and hereinafter, while reaction conditions specifically mentioned above or below are preferred:

In any of the reactions mentioned hereinbefore and hereinafter, protecting groups may be used where appropriate or desired, even if this is not mentioned specifically, to protect functional groups that are not intended to take part in a given reaction, and they can be introduced and/or removed at appropriate or desired stages. Reactions comprising the use of protecting groups are therefore included as possible wherever reactions without specific mentioning of protection and/or deprotection are described in this specification.

Within the scope of this disclosure only a readily removable group that is not a constituent of the particular desired end product of formula I is designated a "protecting group", unless the context indicates otherwise. The protection of functional groups by such protecting groups, the protecting groups themselves, and the reactions appropriate for their removal are described for example in standard reference works, such as J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999, in "The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981, in "Methoden der organischen Chemie" (Methods of Organic Chemistry), Houben Weyl, 4th edition, Volume 15/1, Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H. Jeschkeit, "Aminosäuren, Peptide, Proteine" (Amino acids, Peptides, Proteins), Verlag Chemie, Weinheim, Deerfield Beach, and Basel 1982, and in Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate" (Chemistry of Carbohydrates: Monosaccharides and Derivatives), Georg Thieme Verlag, Stuttgart 1974. A characteristic of protecting groups is that they can be removed readily (i.e. without the occurrence of undesired secondary reactions) for example by

solvolysis, reduction, photolysis or alternatively under physiological conditions (e.g. by enzymatic cleavage).

All the above-mentioned process steps can be carried out under reaction conditions that are known per se, preferably those mentioned specifically, in the absence or, customarily, in the presence of solvents or diluents, preferably solvents or diluents that are inert towards the reagents used and dissolve them, in the absence or presence of catalysts, condensation or neutralizing agents, for example ion exchangers, such as cation exchangers, e.g. in the H⁺ form, depending on the nature of the reaction and/or of the reactants at reduced, normal or elevated temperature, for example in a temperature range of from about -100° C. to about 190° C., preferably from approximately -80° C. to approximately 150° C., for example at from -80 to -60° C., at room temperature, at from -20 to 40° C. or at reflux temperature, under atmospheric pressure or in a closed vessel, where appropriate under pressure, and/or in an inert atmosphere, for example under an argon or nitrogen atmosphere.

The solvents from which those solvents that are suitable for any particular reaction may be selected include those mentioned specifically or, for example, water, esters, such as lower alkyl-lower alkanooates, for example ethyl acetate, ethers, such as aliphatic ethers, for example diethyl ether, or cyclic ethers, for example tetrahydrofuran or dioxane, liquid aromatic hydrocarbons, such as benzene or toluene, alcohols, such as methanol, ethanol or 1- or 2-propanol, nitriles, such as acetonitrile, halogenated hydrocarbons, e.g. as methylene chloride or chloroform, acid amides, such as dimethylformamide or dimethyl acetamide, bases, such as heterocyclic nitrogen bases, for example pyridine or N-methylpyrrolidin-2-one, carboxylic acid anhydrides, such as lower alkanic acid anhydrides, for example acetic anhydride, cyclic, linear or branched hydrocarbons, such as cyclohexane, hexane or isopentane, or mixtures of these, for example aqueous solutions, unless otherwise indicated in the description of the processes. Such solvent mixtures may also be used in working up, for example by chromatography or partitioning.

Intermediates and final products can be worked up and/or purified according to standard methods, e.g. using chromatographic methods, distribution methods, (re-) crystallization, distillation (under normal or reduced pressure), steam distillation and the like.

The invention relates also to those forms of the process in which a compound obtainable as intermediate at any stage of the process is used as starting material and the remaining process steps are carried out, or in which a starting material is formed under the reaction conditions or is used in the form of a derivative, for example in protected form or in the form of a salt, or a compound obtainable by the process according to the invention is produced under the process conditions and processed further in situ. In the process of the present invention those starting materials are preferably used which result in compounds of formula I described as being preferred. Special preference is given to reaction conditions that are identical or analogous to those mentioned in the Examples. The invention also relates to novel intermediates as well as salts thereof where salt-forming groups are present, as well as their synthesis.

Test Assays and Test Methods

The compounds of formula I have valuable pharmacological properties and are useful in the treatment of kinase, especially tie-2 and/or more especially PDGFR, VEGFR-2, c-Abl, Flt3, Ret and/or kit, dependent diseases, e.g., as drugs to treat one or more proliferative diseases.

The usefulness of the compounds of the present invention in the modulation, especially as inhibitors, of protein kinases

can especially and paradigmatically be demonstrated by the following test systems for the protein kinases mentioned as preferred above:

c-Abl, Bcr-Abl

The efficacy of the compounds of formula I as inhibitors of c-Abl protein tyrosine kinase activity can be demonstrated as follows:

An in vitro enzyme assay is performed in 96-well plates as a filter binding assay as described by Geissler et al. in *Cancer Res.* 1992; 52:4492-4498, with the following modifications. The His-tagged kinase domain of c-Abl is cloned and expressed in the baculovirus/Sf9 system as described by Bhat et al. in *J. Biol. Chem.* 1997; 272:16170-16175. A protein of 37 kD (c-Abl kinase) is purified by a two-step procedure over a Cobalt metal chelate column followed by an anion exchange column with a yield of 1-2 mg/L of Sf9 cells (Bhat et al., reference cited). The purity of the c-Abl kinase is >90% as judged by SDS-PAGE after Coomassie blue staining. The assay contains (total volume of 30 μ L): c-Abl kinase (50 ng), 20 mM Tris.HCl, pH 7.5, 10 mM MgCl₂, 10 μ M Na₃VO₄, 1 mM DTT and 0.06 μ Ci/assay [γ ³³P]-ATP (5 μ M ATP) using 30 μ g/mL poly-Ala,Glu,Lys,Tyr-6:2:5:1 (Poly-AEKY, Sigma P1152) in the presence of 1% DMSO. Reactions are terminated by adding 10 μ L of 250 mM EDTA and 30 μ L of the reaction mixture is transferred onto Immobilon-PVDF membrane (Millipore, Bedford, Mass., USA) previously soaked for 5 min with methanol, rinsed with water, then soaked for 5 min with 0.5% H₃PO₄ and mounted on vacuum manifold with disconnected vacuum source. After spotting all samples, vacuum is connected and each well rinsed with 200 μ L 0.5% H₃PO₄. Membranes are removed and washed on a shaker with 0.5% H₃PO₄ (4 times) and once with ethanol. Membranes are counted after drying at ambient temperature, mounting in Packard TopCount 96-well frame, and addition of 10 μ L/well of Microscint TM (Packard). Using this test system, the compounds of formula I show IC₅₀ values of inhibition in the range of 0.002 to 100 μ M, usually between 0.01 and 5 μ M.

Bcr-Abl inhibition can be determined by a capture ELISA as follows: The murine myeloid progenitor cell line 32Dcl3 transfected with the p210 Bcr-Abl expression vector pGDp210Bcr/Abl (32D-bcr/abl) is obtained from J Griffin (Bazzoni et al., *J. Clin Invest.* 98, 521-8 (1996); Zhao et al., *Blood* 90, 4687-9 (1997)). The cells express the fusion bcr-abl protein with a constitutively active alai kinase and proliferate growth factor-independent. The cells are expanded in RPMI 1640 (AMIMED; cat #1-41F01), 10% fetal calf serum, 2 mM glutamine (Gibco) ("complete medium"), and a working stock is prepared by freezing aliquots of 2 \times 10⁶ cells per vial in freezing medium (95% fetal calf serum, 5% dimethylsulfoxide (SIGMA, D-2650). After thawing, the cells are used during maximally 10-12 passages for the experiments. The antibody anti-abl SH3 domain cat. #06-466 from Upstate Biotechnology is used for the ELISA. For detection of bcr-abl phosphorylation, the anti-phosphotyrosine antibody Ab PY20, labelled with alkaline phosphatase (PY10(AP)) from ZYMED (cat. #03-7722) is used. As comparison and reference compound, (N-{5-[4-(4-methyl-piperazino-methyl)-benzoylamido]-2-methylphenyl}-4-(3-pyridyl)-2-pyrimidine-amine, in the form of the methane sulfonate (monomesylate) salt (STI571) (marketed as Gleevec® or Glivec®, Novartis), is used. A stock solution of 10 mM is prepared in DMSO and stored at -20° C. For the cellular assays, the stock solution is diluted in complete medium in two steps (1:100 and 1:10) to yield a starting concentration of 10 μ M followed by preparation of serial threefold dilutions in complete medium. No solubility problems are encountered

using this procedure. The test compounds of formula I are treated analogously. For the assay, 200,000 32D-bcr/abl cells in 50 μ l are seeded per well in 96 well round bottom tissue culture plates. 50 μ l per well of serial threefold dilutions of the test compound are added to the cells in triplicates. The final concentration of the test compound range e.g. from 5 μ M down to 0.01 μ M. Untreated cells are used as control. The compound is incubated together with the cells for 90 min at 37° C., 5% CO₂, followed by centrifugation of the tissue culture plates at 1300 rpm (Beckman GPR centrifuge) and removal of the supernatants by careful aspiration taking care not to remove any of the pelleted cells. The cell pellets are lysed by addition of 150 μ l lysis buffer (50 mM Tris/HCl, pH 7.4, 150 mM sodium chloride, 5 mM EDTA, 1 mM EGTA, 1% NP-40 (non-ionic detergent, Roche Diagnostics GmbH, Mannheim, Germany), 2 mM sodium ortho-vanadate, 1 mM phenylmethyl sulfonyl fluoride, 50 μ g/ml aprotinin and 80 μ g/ml leupeptin) and either used immediately for the ELISA or stored frozen at -20° C. until usage. The anti-abl SH3 domain antibody is coated at 200 ng in 50 μ l PBS per well to black ELISA plates (Packard HTRF-96 black plates; 6005207) overnight at 4° C. After washing 3 \times with 200 μ l/well PBS containing 0.05% Tween 20 (PBST) and 0.5% TopBlock (Juro, Cat. #TB 232010), residual protein binding sites are blocked with 200 μ l/well PBST, 3% TopBlock for 4 h at room temperature, followed by incubation with 50 μ l lysates of untreated or test compound-treated cells (20 μ g total protein per well) for 3-4 h at 4° C. After 3 \times washing, 50 μ l/well PY20(AP) (Zymed) diluted to 0.5 μ g/ml in blocking buffer is added and incubated overnight (4° C.). For all incubation steps, the plates are covered with plate sealers (Costar, cat. #3095). Finally, the plates are washed another three times with washing buffer and once with deionized water before addition of 90 μ l/well of the AP substrate CPDStar RTU with Emerald II. The plates now sealed with Packard Top Seal™-A plate sealers (cat. #6005185) are incubated for 45 min at room temperature in the dark and luminescence is quantified by measuring counts per second (CPS) with a Packard Top Count Microplate Scintillation Counter (Top Count). For the final optimized version of the ELISA, 50 μ l of the lysates of the cells grown, treated and lysed in 96 well tissue culture plates, are transferred directly from these plates to the ELISA plates that are precoated with 50 ng/well of the rabbit polyclonal ant-abl-SH3 domain AB 06-466 from Upstate. The concentration of the anti-phosphotyrosine AB PY20 (AP) can be reduced to 0.2 μ g/ml. Washing, blocking and incubation with the luminescent substrate are as above. The quantification is achieved as follows: The difference between the ELISA readout (CPS) obtained for with the lysates of the untreated 32D-bcr/abl cells and the readout for the assay background (all components, but without cell lysate) is calculated and taken as 100% reflecting the constitutively phosphorylated bcr-abl protein present in these cells. The activity of the compound in the bcr-abl kinase activity is expressed as percent reduction of the bcr-abl phosphorylation. The values for the IC₅₀ are determined from the dose response curves by graphical inter- or extrapolation.

RET

RET kinase inhibition can be determined as follows:

Cloning and expression: The baculovirus donor vector pFB-GSTX3 is used to generate a recombinant baculovirus that expresses the amino acid region 658-1072 (Swiss prot No. Q9BTB0) of the cytoplasmic kinase domain of human RET-Men2A which corresponds to the wild-type kinase domain of RET (wtRET) and RET-Men2B, which differs from the wtRET by the activating mutation in the activation loop M918T. The coding sequence for the cytoplasmic

domain of wtRET is amplified by PCR from a cDNA library using specific primers. RET-Men2B is generated through site-directed mutagenesis resulting in the M918T mutation. The amplified DNA fragments and the pFB-GSTX3 vector are made compatible for ligation by digestion with Sall and KpnI. Ligation of these DNA fragments results in the baculovirus donor plasmids pFB-GX3-RET-Men2A and pFB-GX3-RET-Men2B, respectively.

Production of virus: The baculovirus donor plasmids containing the kinase domains are transfected into the DH10Bac cell line (GIBCO) and the transfected cells are plated on selective agar plates. Colonies without insertion of the fusion sequence into the viral genome (carried by the bacteria) are blue. Single, white colonies are picked and viral DNA (bacmid) is isolated from the bacteria by standard plasmid purification procedures. Sf9 cells or Sf21 cells (American Type Culture Collection) are then transfected in 25 cm² flasks with the viral DNA using Cellfectin reagent.

Protein expression in Sf9 cells: Virus-containing media is collected from the transfected cell culture and used for infection to increase its titer. Virus-containing media obtained after two rounds of infection is used for large-scale protein expression. For large-scale protein expression 100 cm² round tissue culture plates are seeded with 5×10⁷ cells/plate and infected with 1 mL of virus-containing media (approximately 5 MOIs). After 3 days, the cells are scraped off the plate and centrifuged at 500 rpm for 5 minutes. Cell pellets from 10-20, 100 cm² plates are re-suspended in 50 mL of ice-cold lysis buffer (25 mM Tris-HCl, pH 7.5, 2 mM EDTA, 1% NP-40, 1 mM DTT, 1 mM PMSF). The cells are stirred on ice for 15 minutes and then centrifuged at 5,000 rpms for 20 minutes.

Purification of GST-tagged proteins: The centrifuged cell lysate is loaded onto a 2 mL glutathione-sepharose column (Pharmacia) and washed 3× with 10 mL of 25 mM Tris-HCl, pH 7.5, 2 mM EDTA, 1 mM DTT, 200 mM NaCl. The GST-tagged proteins are then eluted by 10 applications (1 mL each) of 25 mM Tris-HCl, pH 7.5, 10 mM reduced-glutathione, 100 mM NaCl, 1 mM DTT, 10% glycerol and stored at -70° C.

Measurement of enzyme activity: Tyrosine protein kinase assays with either purified GST-wtRET or GST-RET-Men2B protein are carried out in a final volume of 30 µL containing 15 ng of either GST-wtRET or GST-RET-Men2B protein, 20 mM Tris-HCl, pH 7.5, 1 mM MnCl₂, 10 mM MgCl₂, 1 mM DTT, 3 µg/mL poly(Glu, Tyr) 4:1, 1% DMSO, 2.0 µM ATP (γ-[³³P]-ATP 0.1 µCi). The activity is assayed in the presence or absence of inhibitors, by measuring the incorporation of ³³P from [γ-³³P] ATP into poly(Glu, Tyr) 4:1. The assay is carried out in 96-well plates at ambient temperature for 15 minutes under conditions described above and terminated by the addition of 20 µL of 125 mM EDTA. Subsequently, 40 µL of the reaction mixture are transferred onto Immobilon-PVDF membrane (Millipore) previously soaked for 5 minutes with methanol, rinsed with water, then soaked for 5 minutes with 0.5% H₃PO₄ and mounted on vacuum manifold with disconnected vacuum source. After spotting all samples, vacuum is connected and each well rinsed with 200 µL 0.5% H₃PO₄. Membranes are removed and washed 4× on a shaker with 1.0% H₃PO₄, once with ethanol. Membranes are counted after drying at ambient temperature, mounting in Packard TopCount 96-well frame, and addition of 10 µL/well of Microscint TM (Packard). IC₅₀ values are calculated by linear regression analysis of the percentage inhibition of each compound in duplicate, at 4 concentrations (usually 0.01, 0.1, 1 and 10 µM). One unit of protein kinase activity is defined as 1 nmole of ³³P transferred from [γ-³³P] ATP to the substrate protein/minute/mg of protein at 37° C. The compounds of

formula I here show IC₅₀ values in the range between 0.07 and 20 µM, especially between 0.1 and 5 µM.

PDGFR

The efficacy of the compounds of formula I as inhibitors of c-Kit and PDGFR tyrosine kinase activity can be demonstrated as follows:

BaF3-Tel-PDGFRbeta is a BaF3 murine proB-cell lymphoma cell derivative [the BaF3 cell line is available from the German Collection of Microorganisms and Cell Cultures (DSMZ), Braunschweig, Germany] that has been rendered IL-3-independent by stable transduction with Tel-fusion-activated PDGFR-β wild-type (Golub T. R. et al., Cell 77(2): 307-316, 1994) or D816V-mutation-activated c-kit, respectively. Cells are cultured in RPMI-1640 (Animed #1-14F01-I) supplemented with 2% L-glutamine (Animed #5-10K50-H) and 10% fetal calf serum (FCS, Animed #2-01F16-I). Wild-type, untransfected BaF3 cells are maintained in above medium plus 10 U/ml IL-3 (mouse Interleukin-3, Roche #1380745).

Cells are diluted in fresh medium to a final density of 3×10⁵ cells per ml and 50 µl aliquots seeded into 96-well plates (1.5×10⁴ cells per well). 50 µl 2× compound solutions are added. As internal control, the kinase inhibitor PKC412 is routinely used. Control cells treated with DMSO (0.1% final concentration) serve as growth reference (set as 100% growth). In addition, a plate blank value is routinely determined in a well containing only 100 µl of medium and no cells. IC₅₀ determinations are performed based on eight 3-fold serial dilutions of the test compound, starting at 10 µM. Following incubation of the cells for 48 h at 37° C. and 5% CO₂, the effect of inhibitors on cell viability is assessed by the resazurin sodium salt dye reduction assay (commercially known as AlamarBlue assay) basically as previously described (O'Brien J. et al., Eur. J. Biochem. 267: 5421-5426, 2000). 10 µl of AlamarBlue is added per well and the plates incubated for 6 h at 37° C. and 5% CO₂. Thereafter, fluorescence is measured using a Gemini 96-well plate reader (Molecular Devices) with the following settings: Excitation 544 nm and Emission 590 nm. Acquired raw data are exported to Excel-file format. For data analysis, the plate blank value is subtracted from all data points. The anti-proliferative effect of a compound by the AlamarBlue read-out was then calculated as percentage of the value of the control cells set as 100%. IC₅₀ values are determined using XLfit software program. The compounds of formula I show an IC₅₀ for PDGFR-β in the range of 0.001 to 20 µM, especially between 0.002 and 0.1 µM.

c-Kit can be measured analogously using BaF3-KitD816V murine proB lymphoma cell derivatives.

FLT3 Receptor Kinase

To search for FLT3-targeted compounds, two different kinds of assays can be employed: Flt3 kinase activity is determined as follows: The baculovirus donor vector pFbacG01 (GIBCO) is used to generate a recombinant baculovirus expressing the amino acid region from amino acids 563-993 of the cytoplasmic kinase domain of human Flt3. The coding sequence for the cytoplasmic domain of Flt3 is amplified by PCR from human c-DNA libraries (Clontech). The amplified DNA fragments and the pFbacG01 vector are made compatible for ligation by digestion with BamHI and HindIII. Ligation of these DNA fragments results in the baculovirus donor plasmid Flt-3(1.1). The production of the viruses, the expression of protein in Sf9 cells and the purification of the GST-fused protein is performed as follows:

Production of virus: Transfer vector(pFbacG01-Flt-3) containing the Flt3-kinase domain is transfected into the DH10Bac cell line (GIBCO) and the transfected cells are

plated on selective agar plates. Colonies without insertion of the fusion sequence into the viral genome (carried by the bacteria) are blue. Single white colonies are picked and viral DNA (bacmid) is isolated from the bacteria by standard plasmid purification procedures. Sf9 or Sf21 cells (American Type Culture Collection) are then transfected in flasks with the viral DNA using Cellfectin reagent.

Determination of small scale protein expression on Sf9 cells: Virus containing medium is collected from the transfected cell culture and used for infection to increase its titre. Virus containing medium obtained after two rounds of infection is used for large-scale protein expression. For large-scale protein expression, 100 cm² round tissue culture plates are seeded with 5×10⁷ cells/plate and infected with 1 ml of virus-containing medium (approximately 5 MOIs). After 3 days, the cells are scraped off the plate and centrifuged at 500 rpm for 5 min. Cell pellets from 10-20 plates with each 100 cm² are resuspended in 50 ml of ice-cold lysis buffer (25 mM Tris-HCl, pH 7.5, 2 mM EDTA, 1% NP-40, 1 mM DTT, 1 mM PMSF). The cells are stirred on ice for 15 min and then centrifuged at 5000 rpm for 20 min.

Purification of GST-tagged protein: The centrifuged cell lysate is loaded onto a 2 ml glutathione-sepharose column (Pharmacia) and washed three times with 10 ml of 25 mM Tris-HCl, pH 7.5, 2 mM EDTA, 1 mM DTT, 200 mM NaCl. The GST-tagged protein is then eluted by 10 applications (1 ml each) of 25 mM Tris-HCl, pH 7.5, 10 mM reduced glutathione, 100 mM NaCl, 1 mM DTT, 10% glycerol, and stored at -70° C.

Measurement of Enzyme activity: Tyrosine protein kinase assays with purified GST-Flt2 are carried out in a final volume of 30 µl containing 200-1800 ng of enzyme protein (depending on the specific activity), 20 mM Tris-HCl, pH 7.6, 3 mM MnCl₂, 3 mM MgCl₂, 1 mM DTT, 10 µM Na₃VO₄, 3 µg/ml poly(Glu, Tyr) 4:1, 1% DMSO, 6.0 µM ATP and 0.1 µCi [³³P]ATP. The activity is assayed in the presence or absence of inhibitors, by measuring the incorporation of ³³P from [³³P]ATP into the poly(Glu, Tyr) substrate. The assay (30 µl per well) is carried out in 96-well plates at ambient temperature for 20 min under conditions described below and terminated by the addition of 20 µl of 125 mM EDTA. Subsequently, 40 µl of each reaction mixture is transferred onto Immobilon-PVDF membrane (Millipore, Bedford, Mass., USA) previously soaked for 5 min with methanol, rinsed with water, then soaked for 5 min with 0.5% H₃PO₄ and mounted on vacuum manifold with disconnected vacuum source. After spotting all samples, vacuum is connected and each well rinsed with 200 µl 0.5% H₃PO₄. Membranes are removed and washed 4× on a shaker with 1.0% H₃PO₄, once with ethanol. Membranes are then counted individually after drying at ambient temperature, mounting in Packard TopCount 96-well frame and addition of 10 µl/well Microscint TM (Packard). IC₅₀ values are calculated by linear regression analysis of the percentage inhibition of each compound in duplicate, at four concentrations (usually 0.01, 0.1, 1 and 10 µM). One unit of protein kinase is defined as 1 nmole of ³³P ATP transferred from [³³P]ATP to the substrate polypeptide per minute per mg of protein at 37° C. The compounds of the present invention here show IC₅₀ values in the range between 0.03 and 100 µM, preferably between 0.2 and 10 µM.

Alternatively or in addition, a cell based assay can be utilised to identify inhibitors of mutant FLT3 tyrosine kinase receptors. The general technique involves comparing the effects of possible inhibitors on cell lines that depended on mutant FLT3 for proliferation, versus cell lines that do not depend on mutant FLT3 for proliferation. Cell lines expressing two different forms of mutated, activated FLT3 are used:

Ba/F3-FLT3-ITD cells expressing a FLT3 mutant with an "Internal Tandem Duplication" (ITD) within the juxtamembrane domain of the receptor.

Ba/F3-FLT3-D835Y cells expressing an FLT3 receptor containing a mutation converting Asparagine at position 835 to Tyrosine.

Tested compounds of the present invention can be shown to inhibit proliferation of both Ba/F3-FLT3-ITD and Ba/F3-D835Y cells while on the other hand they usually do not inhibit growth of untransformed Ba/F3 cells at concentrations of up to 500 nM, and the growth inhibitory effects of a compound of the present invention on Ba/F3-FLT3-ITD cells can be reversed by the addition of high concentrations of IL-3 to provide an alternative viability signal. At the concentrations required to inhibit the proliferation of FLT3-dependent cell-lines, compounds of the present invention can be shown to be not cytotoxic against several human leukemia and lymphoma cell lines that do not have mutant FLT3 receptors (hyperactivated kinases), suggesting that the drug has an unexpected high degree of specificity as a cytotoxic agent. Overall, these results indicate that compounds present invention can be potent inhibitors of mutant FLT3 receptor tyrosine kinase activity and are a promising candidate for use in the treatment in patients with mutant FLT3 receptors. In particular, tested compounds of the present invention can be shown to inhibit the activity of FLT3 receptor tyrosine kinase activity in concentrations in the range of 0.00015 to 1.0 µM.

IGF1R

BaF3-Tel-IGF1R are BaF3 murine proB-cell lymphoma cell derivatives [the BaF3 cell line is available from the German Collection of Microorganisms and Cell Cultures (DSMZ), Braunschweig, Germany] that have been rendered IL-3-independent by stable transduction with an activating fusion-protein consisting of human Tel(aa1-452, UniProt: P41212; GenBank: U11732), a Ser-Arg-linker, and human IGF1R(aa976-1367, UniProt: P08069; GenBank: X04434) (Dr. J. Griffin, DanaFarber Cancer Institute, Boston, USA, unpublished). Cells are cultured in RPMI-1640 (Animed #1-14F01-I) supplemented with 2% L-glutamine (Animed #5-10K50-H) and 10% fetal calf serum (FCS, Animed #2-01F16-I). Wild-type, untransfected BaF3 cells are maintained in above medium plus 10 U/ml IL-3 (mouse Interleukin-3, Roche #1380745).

Cells are diluted in fresh medium to a final density of 3×10⁵ cells per ml and 50 µl aliquots seeded into 96-well plates (1.5×10⁴ cells per well). 50 µl 2× compound solutions are added. As internal control, the kinase inhibitor PKC412 is routinely used. Control cells treated with DMSO (0.1% final concentration) serve as growth reference (set as 100% growth). In addition, a plate blank value is routinely determined in a well containing only 100 µl of medium and no cells. IC₅₀ determinations are performed based on eight 3-fold serial dilutions of the test compound, starting at 10 µM. Following incubation of the cells for 48 h at 37° C. and 5% CO₂, the effect of compounds on cell viability is assessed by the resazurin sodium salt dye reduction assay (commercially known as AlamarBlue assay) basically as previously described (O'Brien J. et al., Eur. J. Biochem. 267: 5421-5426, 2000). 10 µl of AlamarBlue is added per well and the plates incubated for 6 h at 37° C. and 5% CO₂. Thereafter, fluorescence is measured using a Gemini 96-well plate reader (Molecular Devices) with the following settings: Excitation 544 nm and Emission 590 nm.

Acquired raw data are exported to Excel-file format. For data analysis, the plate blank value is subtracted from all data points. Residual cell viability for each compound concentration is expressed as percentage of the value measured for the

vehicle-treated control cells (set as 100%). IC₅₀ values (reduction of cell viability by 50%) are determined using the Milt curve-fitting software.

VEGF-R (KDR) Autophosphorylation

The inhibition of VEGF-induced receptor autophosphorylation can be confirmed with *in vitro* experiments in cells such as transfected CHO cells, which permanently express human VEGF-R2 (KDR), are seeded in complete culture medium (with 10% fetal calf serum=FCS) in 6-well cell-culture plates and incubated at 37° C. under 5% CO₂ until they show about 80% confluency. The compounds to be tested are then diluted in culture medium (without FCS, with 0.1% bovine serum albumin) and added to the cells. (Controls comprise medium without test compounds). After two hours of incubation at 37° C., recombinant VEGF is added; the final VEGF concentration is 20 ng/ml. After a further five minutes incubation at 37° C., the cells are washed twice with ice-cold PBS (phosphate-buffered saline) and immediately lysed in 100 µl lysis buffer per well. The lysates are then centrifuged to remove the cell nuclei, and the protein concentrations of the supernatants are determined using a commercial protein assay (BIORAD). The lysates can then either be immediately used or, if necessary, stored at -20° C.

A sandwich ELISA is carried out to measure the VEGF-R2 phosphorylation: a monoclonal antibody to VEGF-R2 (for example Mab 1495.12.14; prepared by H. Towbin, Novartis or comparable monoclonal antibody) is immobilized on black ELISA plates (OptiPlate™ HTRF-96 from Packard). The plates are then washed and the remaining free protein-binding sites are saturated with 3% TopBlock® (Juro, Cat. #TB232010) in phosphate buffered saline with Tween 20® (polyoxyethylen(20)sorbitane monolaurate, ICI/Uniquema) (PBST). The cell lysates (20 µg protein per well) are then incubated in these plates overnight at 4° C. together with an antiphosphotyrosine antibody coupled with alkaline phosphatase (PY20:AP from Zymed). The plates are washed again and the binding of the antiphosphotyrosine antibody to the captured phosphorylated receptor is then demonstrated using a luminescent AP substrate (CDP-Star, ready to use, with Emerald II; Applied Biosystems). The luminescence is measured in a Packard Top Count Microplate Scintillation Counter. The difference between the signal of the positive control (stimulated with VEGF) and that of the negative control (not stimulated with VEGF) corresponds to VEGF-induced VEGF-R2 phosphorylation (=100%). The activity of the tested substances is calculated as percent inhibition of VEGF-induced VEGF-R2 phosphorylation, wherein the concentration of substance that induces half the maximum inhibition is defined as the IC₅₀ (inhibitory dose for 50% inhibition). The compounds of the present invention here show an IC₅₀ in the range of 0.01 to 20 µM, especially between 0.1 and 1.0 µM.

VEGF-R1

VEGF-R1 inhibition can be shown as follows: the test is conducted using Flt-1 VEGF-receptor tyrosine kinase. The detailed procedure is as follows: 30 µl kinase solution (kinase domain of Flt-1, Shibuya et al., *Oncogene* 5, 519-24 [1990], according to the specific activity, in order to achieve an activity of 4000-6000 counts per minute [cpm] in the sample without inhibitor) in 20 mM Tris.HCl pH 7.5, 3 mM manganese dichloride (MnCl₂), 3 mM magnesium chloride (MgCl₂) and 3 µg/ml poly(Glu, Tyr) 4:1 (Sigma, Buchs, Switzerland), 8 µM [³³P]-ATP (0.2 µCi/batch), 1% dimethyl sulfoxide, and 0 to 50 µM of the compound to be tested are incubated together for 10 minutes at room temperature. The reaction is then ended by the addition of 10 µl 0.25 M ethylenediamine-tetraacetate (EDTA) pH 7. Using a multichannel dispenser

(LAB SYSTEMS, USA), an aliquot of 20 µl is applied to a PVDF (=polyvinyl difluoride) Immobilon P membrane (Millipore, USA), which is incorporated into a Millipore microtitre filter manifold, and connected to a vacuum. Following complete elimination of the liquid, the membrane is washed 4 times successively in a bath containing 0.5% phosphoric acid (H₃PO₄), incubated for 10 minutes each time while shaking, then mounted in a Hewlett Packard TopCount Manifold and the radioactivity measured after the addition of 10 µl Microscint® (β-scintillation counter liquid; Packard USA). IC₅₀-values are determined by linear regression analysis of the percentages for the inhibition of each compound in three concentrations (as a rule 0.01, 0.1, and 1 µM).

The efficacy of compounds of present invention as inhibitors of tumor growth can be demonstrated using various *in vivo* models, for example, as follows:

For example, in order to test whether a compound of the present invention, e.g. according to one of the Examples given below, inhibits VEGF-mediated angiogenesis *in vivo*, its effect on the angiogenic response induced by VEGF in a growth factor implant model in mice is tested: A porous Teflon chamber (volume 0.5 mL) is filled with 0.8% w/v agar containing heparin (20 units/ml) with or without growth factor (2 µg/ml human VEGF) is implanted subcutaneously on the dorsal flank of C57/C6 mice. The mice are treated with the test compound (e.g. 25, 50 or 100 mg/kg p.o. once daily) or vehicle starting on the day of implantation of the chamber and continuing for 4 days after. At the end of the treatment, the mice are killed, and the chambers are removed. The vascularized tissue growing around the chamber is carefully removed and weighed, and the blood content is assessed by measuring the hemoglobin content of the tissue (Drabkins method; Sigma, Deisenhofen, Germany). It has been shown previously that these growth factors induce dose-dependent increases in weight and blood content of this tissue growing (characterized histologically to contain fibroblasts and small blood vessels) around the chambers and that this response is blocked by antibodies that specifically neutralize VEGF (see Wood J M et al., *Cancer Res.* 60(8), 2178-2189, (2000); and Schlaeppli et al., *J. Cancer Res. Clin. Oncol.* 125, 336-342, (1999)). With such types of model, it is possible to show inhibition of tumor growth with compounds of the present invention if tested.

Tie-2 Receptor Autophosphorylation

The inhibition of Tie-2 receptor autophosphorylation can be confirmed with an *in vitro* experiment in cells such as transfected COS cells (ATCC Number: CRL-1651), which permanently express human Tie-2 (SwissProt AccNo Q02763), are seeded in complete culture medium (with 10% fetal calf serum=FCS) in 6-well cell-culture plates and incubated at 37° C. under 5% CO₂ until they show about 90% confluency. The compounds to be tested are then diluted in culture medium (without FCS, with 0.1% bovine serum albumin) and added to the cells.

Controls comprise medium without test compounds. After 40 min of incubation at 37° C., ortho vanadate is added to give the final concentration of 10 mM. After a further incubation for 20 minutes at 37° C., the cells are washed twice with ice-cold PBS (phosphate-buffered saline) and immediately lysed in 100 µl lysis buffer per well. The lysates are then centrifuged to remove the cell nuclei, and the protein concentrations of the supernatants are determined using a commercial protein assay (BIORAD). The lysates can then either be immediately used or, if necessary, stored at -20° C.

A sandwich ELISA is carried out to measure the Tie-2 phosphorylation: a monoclonal antibody to Tie-2 (for example anti-Tie2 clone AB33, Upstate, Cat Nr. 05-584 or

comparable monoclonal antibody) is immobilized using 0.1 ml of a 2 µg/ml solution on black ELISA plates (OptiPlate™ HTRF-96 from Packard). The plates are then washed and the remaining free protein-binding sites are saturated with 3% TopBlock® (Juro, Cat. #TB232010) in phosphate buffered saline with Tween 20® (polyoxyethylen(20)sorbitane monolaurate, ICI/Uniquema) (PBST). The cell lysates (100 µg protein per well) are then incubated in these plates overnight at 4° C. together with an antiphosphotyrosine antibody coupled with alkaline phosphatase (PY20:AP from Zymed). The (plates are washed again and the) binding of the antiphosphotyrosine antibody to the captured phosphorylated receptor is then demonstrated using a luminescent AP substrate (CDP-Star, ready to use, with Emerald II; Applied Bio-systems). The luminescence is measured in a Packard Top Count Microplate Scintillation Counter. The difference between the signal of the positive control (stimulated with vanadate) and that of the negative control (not stimulated) corresponds to maximum Tie-2 phosphorylation (=100%). The activity of the tested substances is calculated as percent inhibition of maximum Tie-2 phosphorylation, and the concentration of substance that induces half the maximum inhibition is defined as the IC₅₀ (inhibitory dose for 50% inhibition). For compounds of the present invention, preferably IC₅₀ values in the range from 0.05 to 20 µM can be found, e.g. more preferably from 0.1 to 10 µM.

The compounds of the present invention show activity in test assays and test methods as described herein and are therefore indicated for use as pharmaceuticals, e.g. for the treatment of disorders mediated by protein kinase activity.

In view of their protein kinase modulating (especially inhibiting) properties and/or possibly other not yet known mechanisms, the use of the present compounds in the treatment of a variety of proliferative diseases, including those mentioned below, and/or diseases that depend on (especially inappropriate) protein kinase activity is possible.

For example, compounds of the present invention can be used in the treatment of leukemias (of adult or childhood type), especially chronic myelogenous leukaemia (CML), AML (acute myeloid leukemia), AML with trilineage myelodysplasia (AML/TMDS), acute lymphoblastic leukemia (ALL), myelodysplastic syndrome (MDS), as well as MLL (mixed-lineage leukemia); different (especially primary, but also derived) solid tumors (including benign or especially malignant types) such as sarcoma (e.g. Ewing sarcoma, Kaposi's sarcoma or soft part sarcomas such as Dermatofibrosarcoma protuberans), gastrointestinal stromal tumors (GIST), seminoma, carcinoids, mast cell tumors, lung carcinomas, such as small or large cell lung carcinoma, bronchial carcinomas, such as small cell bronchial carcinoma, seminomas, dysgerminomas, testicular intraepithelial neoplasias, melanomas, mamma carcinomas, neuroblastomas, papillary/follicular thyroid carcinoma, malign lymphomas, Non Hodgkin's lymphoma, multiple endocrine neoplasia type 2 (MEN 2), pheochromocytoma, thyroid carcinoma, e.g. medullary thyroid carcinoma, parathyroid hyperplasia/adenoma, mamma carcinoma, colon cancer, colorectal adenoma, ovarian cancer, prostate carcinoma, glioblastoma, brain tumors, prostate carcinoma (also including adenocarcinomas and bone metastasis), malign gliomas (anaplastic astrocytomas/glioblastomas), pancreatic cancer, malignant pleural mesothelioma, haemangioblastoma, haemangioma, carcinoma of the kidney, liver, adrenal gland, bladder, stomach (especially gastric tumors), rectum, vagina, cervix, endometrium, multiple myeloma, tumors of the neck and head, e.g. squamous carcinoma of the head and neck, including neoplasias, especially

of epithelial character, e.g. in the case of mammary carcinoma, malignant nephrosclerosis; or of other hyperplasias or proliferative diseases, such as mastocytosis, associated myeloproliferative syndrome, Urticaria Pigmentosa, an epidermal hyperproliferation (other than cancer), especially psoriasis; prostate hyperplasia; inflammatory diseases, such as rheumatoid or rheumatic inflammatory diseases, especially arthritis, such as rheumatoid arthritis, other chronic inflammatory disorders, such as chronic asthma, arterial or post-transplantational atherosclerosis, other diseases associated with deregulated angiogenesis, e.g. fibrosis (especially pulmonary, but also other types of fibrosis, such as renal fibrosis), angiogenesis, smooth muscle proliferation in the blood vessels, such as stenosis or (e.g. stent-induced) restenosis following angioplasty; (e.g. ischemic) retinopathies, (for example, age related) macula degeneration, other eye diseases, such as diabetic retinopathy and neovascular glaucoma; renal diseases, such as glomerulonephritis; diabetic nephropathy; inflammatory bowel disease, such as Crohn's disease, thrombotic microangiopathic syndromes; (e.g. chronic) transplant rejections and glomerulopathy; fibrotic diseases, such as cirrhosis of the liver; mesangial cell-proliferative diseases and or injuries of the nerve tissue.

In addition, a compound of the present invention can be useful as immunosuppressants, e.g. as an aid in scar-free wound healing, and for treating age spots and contact dermatitis.

In spite of the mechanism mentioned in the "Background of the Invention", surprisingly also tie-2 inhibition can be shown to be useful against proliferative diseases, especially solid tumors.

Disorders as used herein include diseases.

Disorders which are mediated by protein kinase activity and which are prone to be successfully treated with protein kinase activity mediators, e.g. modulators, e.g. inhibitors, such as the compounds of the present invention, include e.g. disorders wherein the activity of one or more protein kinases plays a causal or contributory role, e.g. such as disorders associated with the interruption of the binding of the protein kinase to its substrate, e.g. disorders that respond to protein kinase modulation, especially inhibition, by a compound of the present invention.

Preferably protein kinase activity which is prone to be mediated by a compound of the present invention is activity from protein kinases, such as a protein tyrosine kinase, e.g. one or more protein kinases selected from the group consisting of tie-2 and/or PDGFR, VEGFR-2, c-Abl, Flt3, Ret, kit and IGF1R, e.g. and/or one or more altered or mutated forms of any one or more of these.

Disorders mediated by protein kinase activity, e.g. mediated by compounds of the present invention, e.g. include, but are not limited to, disorders or disorders associated with leukemias, solid tumors, or other hyperplasias or proliferative diseases, inflammatory diseases, chronic inflammatory disorders, diseases associated with deregulated angiogenesis, eye diseases, renal diseases, inflammatory bowel disease, thrombotic microangiopathic syndromes; (chronic) transplant rejections and glomerulopathy, fibrotic diseases, mesangial cell-proliferative diseases injuries of the nerve tissue. the respiratory tract and lung, rheumatic disorders,

transplantation,
thrombotic microangiopathic syndromes,
mesangial cell-proliferative disease,
injuries of the nerve tissue,
immunosuppression.

Preferably the compounds of the present invention may be used as drugs for the treatment of one or more proliferative disorders.

In another aspect the present invention provides a compound of the present invention for use as a pharmaceutical,
the use of a compound of the present invention as a pharmaceutical,
e.g. for the treatment of disorders mediated by protein kinase activity.

For pharmaceutical use one or more compounds of the present invention may be used, e.g. one, or a combination of two or more compounds of the present invention, preferably one compound of the present invention is used.

A compound of the present invention may be used as a pharmaceutical in the form of a pharmaceutical composition.

In another aspect the present invention provides a pharmaceutical composition comprising a compound of the present invention in association with at least one pharmaceutically acceptable excipient, e.g. appropriate carrier and/or diluent, e.g. including fillers, binders, disintegrants, flow conditioners, lubricants, sugars or sweeteners, fragrances, preservatives, stabilizers, wetting agents and/or emulsifiers, solubilizers, salts for regulating osmotic pressure and/or buffers.

In another aspect the present invention provides a pharmaceutical composition of the present invention for use of treating disorders which are mediated by protein kinase activity.

the use of a pharmaceutical composition of the present invention for treating disorders which are mediated by protein kinase activity.

a compound of the present invention for use of treating disorders which are mediated by protein kinase activity.

In a further aspect the present invention provides a method of treating disorders which are mediated by protein kinase activity, e.g. including disorders as specified above, which treatment comprises administering to a subject in need of such treatment a therapeutically effective amount of a compound of the present invention; e.g. in the form of a pharmaceutical composition.

“A subject in need of such treatment” as used e.g. herein includes a patient, e.g. an animal, e.g. a warm-blooded animal, more preferably a mammal, especially a human.

“A therapeutically effective amount” is preferably an amount which is effective against said disorder(s).

In another aspect the present invention provides a compound of the present invention for the manufacture of a medicament,

the use of a compound of the present invention for the manufacture of a medicament,
e.g. a pharmaceutical composition, for the treatment of disorders, which are mediated by protein kinase activity.

Treatment of disorders (diseases) as used herein includes prophylaxis (prevention). For such treatment, the appropriate dosage will, of course, vary depending upon, for example, the chemical nature and the pharmacokinetic data of a compound of the present invention used, the individual host, e.g. the body weight, the age and the individual condition of a subject in need of such treatment, the mode of administration and the nature and severity of the conditions being treated. However, in general, for satisfactory results in larger mammals, for example humans, an indicated daily dosage includes a range

from about 0.0001 g to about 1.5 g, such as 0.001 g to 1.5 g;

from about 0.001 mg/kg body weight to about 20 mg/kg body weight, such as 0.01 mg/kg body weight to 20 mg/kg body weight,

for example administered in divided doses up to four times a day.

Usually, children may receive half of the adult dose.

The pharmaceutical compositions comprise from approximately 1% to approximately 96%, preferably from approximately 20% to approximately 95%, active ingredient.

A compound of the present invention may be administered by any conventional route, for example enterally, e.g. including nasal, buccal, rectal, oral administration; parenterally, e.g. including intravenous, intraarterial, intramuscular, intracardiac, subcutaneous, intraosseous infusion, transdermal (diffusion through the intact skin), transmucosal (diffusion through a mucous membrane), inhalational administration; topically; e.g. including epicutaneous, intranasal, intratracheal administration; intraperitoneal (infusion or injection into the peritoneal cavity); epidural (peridural) (injection or infusion into the epidural space); intrathecal (injection or infusion into the cerebrospinal fluid); intravitreal (administration via the eye); or via medical devices, e.g. for local delivery, e.g. stents;

e.g. in form of coated or uncoated tablets, capsules, (injectable) solutions, solid solutions, suspensions, dispersions, solid dispersions; e.g. in the form of ampoules, vials, in the form of creams, gels, pastes, inhaler powder, foams, tinctures, lip sticks, drops, sprays, or in the form of suppositories.

For topical use, e.g. including administration to the eye, satisfactory results may be obtained with local administration of a 0.5-10%, such as 1-3% concentration of active substance several times daily, e.g. 2 to 5 times daily.

The compounds of the present invention may be administered in the form of a pharmaceutically acceptable salt, or in free form; optionally in the form of a solvate. A compound of the present invention in the form of a salt and/or in the form of a solvate exhibits the same order of activity as a compound of the present invention in free form.

A compound of the present invention may be used for any method or use as described herein alone or in combination with one or more, at least one, other, second drug substance.

In another aspect the present invention provides

A combination of a compound of the present invention with at least one second drug substance;

A pharmaceutical combination comprising a compound of the present invention in combination with at least one second drug substance;

A pharmaceutical composition comprising a compound of the present invention in combination with at least one second drug substance and one or more pharmaceutically acceptable excipient(s);

A compound of the present invention in combination with at least one second drug substance, e.g. in the form of a pharmaceutical combination or composition, for use in any method as defined herein, e.g.

A combination, a pharmaceutical combination or a pharmaceutical composition, comprising a compound of the present invention and at least one second drug substance for use as a pharmaceutical;

The use as a pharmaceutical of a compound of the present invention in combination with at least one second drug substance, e.g. in the form of a pharmaceutical combination or composition;

The use of a compound of the present invention for the manufacture of a medicament for use in combination with a second drug substance

A method for treating disorders mediated by protein kinase activity in a subject in need thereof, comprising co-administering, concomitantly or in sequence, a therapeutically effective amount of a compound of the present invention and at least one second drug substance, e.g. in the form of a pharmaceutical combination or composition;

A compound of the present invention in combination with at least one second drug substance, e.g. in the form of a pharmaceutical combination or composition, for use in the preparation of a medicament for use in disorders mediated by protein kinase activity.

Combinations include fixed combinations, in which a compound of the present invention and at least one second drug substance are in the same formulation; kits, in which a compound of the present invention and at least one second drug substance in separate formulations are provided in the same package, e.g. with instruction for co-administration; and free combinations in which a compound of the present invention and at least one second drug substance are packaged separately, but instruction for concomitant or sequential administration are given.

In another aspect the present invention provides

A pharmaceutical package comprising a first drug substance which is a compound of the present invention and at least one second drug substance, beside instructions for combined administration;

A pharmaceutical package comprising a compound of the present invention beside instructions for combined administration with at least one second drug substance;

A pharmaceutical package comprising at least one second drug substance beside instructions for combined administration with a compound of the present invention.

Treatment with combinations according to the present invention may provide improvements compared with single treatment.

In another aspect the present invention provides

A pharmaceutical combination comprising an amount of a compound of the present invention and an amount of a second drug substance, wherein the amounts are appropriate to produce a synergistic therapeutic effect;

A method for improving the therapeutic utility of a compound of the present invention comprising co-administering, e.g. concomitantly or in sequence, of a therapeutically effective amount of a compound of the present invention and a second drug substance.

A method for improving the therapeutic utility of a second drug substance comprising co-administering, e.g. concomitantly or in sequence, of a therapeutically effective amount of a compound of the present invention and a second drug substance.

A combination of the present invention and a second drug substance as a combination partner may be administered by any conventional route, for example as set out above for a compound of the present invention. A second drug may be administered in dosages as appropriate, e.g. in dosage ranges which are similar to those used for single treatment, or, e.g. in case of synergy, even below conventional dosage ranges.

Pharmaceutical compositions according to the present invention may be manufactured according, e.g. analogously, to a method as conventional, e.g. by mixing, granulating, coating, dissolving or lyophilizing processes. Unit dosage forms may contain, for example, from about 0.1 mg to about 1500 mg, such as 1 mg to about 1000 mg.

Pharmaceutical compositions comprising a combination of the present invention and pharmaceutical compositions comprising a second drug as described herein, may be provided as appropriate, e.g. according, e.g. analogously, to a method as conventional, or as described herein for a pharmaceutical composition of the present invention.

Solutions of the active ingredient, and also suspensions, and especially isotonic aqueous solutions or suspensions, are preferably used, it being possible, for example in the case of lyophilized compositions that comprise the active ingredient alone or together with a carrier, for example mannitol, for such solutions or suspensions to be produced prior to use. The pharmaceutical compositions may be sterilized and/or may comprise excipients, for example preservatives, stabilizers, wetting and/or emulsifying agents, solubilizers, salts for regulating the osmotic pressure and/or buffers, and are prepared in a manner known per se, for example by means of conventional dissolving or lyophilizing processes. The said solutions or suspensions may comprise viscosity-increasing substances, such as sodium carboxymethylcellulose, carboxymethylcellulose, dextran, polyvinylpyrrolidone or gelatin.

Pharmaceutical compositions for oral administration can be obtained by combining the active ingredient with solid carriers, if desired granulating a resulting mixture, and processing the mixture, if desired or necessary, after the addition of appropriate excipients, into tablets, dragée cores or capsules. It is also possible for them to be incorporated into plastics carriers that allow the active ingredients to diffuse or be released in measured amounts.

By the term "second drug substance" is meant a chemotherapeutic drug, especially any chemotherapeutic agent other than a compound of the present invention.

For example, a second drug substance as used herein includes an anticancer drug. Anticancer drugs e.g include, but are not limited to, aromatase inhibitors; antiestrogens; topoisomerase I inhibitors; topoisomerase II inhibitors; microtubule active agents; alkylating agents; histone deacetylase inhibitors; compounds which induce cell differentiation processes; cyclooxygenase inhibitors; MMP inhibitors; mTOR inhibitors; antineoplastic antimetabolites; platin compounds; compounds targeting/decreasing a protein or lipid kinase activity and further anti-angiogenic compounds; compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase; gonadorelin agonists; anti-androgens; methionine aminopeptidase inhibitors; bisphosphonates; biological response modifiers; antiproliferative antibodies; heparanase inhibitors; inhibitors of Ras oncogenic isoforms; telomerase inhibitors; proteasome inhibitors; agents used in the treatment of hematologic malignancies; compounds which target, decrease or inhibit the activity of Flt-3; Hsp90 inhibitors; and temozolomide (TEMODAL®).

For the treatment of acute myeloid leukemia (AML), compounds of formula I can be used in combination with standard leukemia therapies, especially in combination with therapies used for the treatment of AML. In particular, compounds of formula I can be administered in combination with e.g. farnesyl transferase inhibitors and/or other drugs useful for the treatment of AML, such as Daunorubicin, Adriamycin, Ara-C, VP-16, Teniposide, Mitoxantrone, Idarubicin, Carboplatinum and PKC412.

The structure of the active agents identified by code nos., generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Patents International (e.g. IMS World Publications).

A second drug substance which can be used in combination with a compound of the present invention may be prepared and administered as appropriate, e.g. such as conventional, e.g. such as in the documents cited above.

A compound of the present invention may also be used to advantage in combination with known therapeutic processes, e.g., the administration of hormones or especially radiation.

A compound of formula I may in particular be used as a radiosensitizer, especially for the treatment of tumors which exhibit poor sensitivity to radiotherapy.

If the compounds of the present invention are administered in combination with other drugs dosages of the co-administered second drug will of course vary depending on the type of co-drug employed, on the specific drug employed, on the condition being treated, as in case of a compound of the present invention. In general dosages similar than those as provided by the second drug supplier may be appropriate

The following Examples serve to illustrate the invention without limiting the scope thereof.

Temperatures are indicated in degrees Celsius ($^{\circ}$ C.). Unless otherwise indicated, the reactions take place at rt.

TLC conditions: The R_f values which indicate the ratio of the distance moved by each substance to the distance moved by the eluent front are determined on silica gel thin-layer plates 5x10 cm TLC plates, silica gel F₂₅₄ (Merck, Darmstadt, Germany) by thin-layer chromatography using the solvent systems indicated below.

Analytical HPLC Conditions:

System 1

Linear gradient 20-100% CH₃CN in 5 min+1.5 min 100% CH₃CN (0.1% TFA); detection at 215 nm, flow rate 1 mL/min at 30 $^{\circ}$ C. Column: Nucleosil 100-3 C18 (70x4.0 mm)

System 2

Linear gradient 5-95% CH₃CN in 2.20 min+0.5 min 95% CH₃CN (0.1% TFA); detection at 215 nm, flow rate 2 mL/min at 35 $^{\circ}$ C. Column: Sun Fire (waters) 3.5 μ m C18 (3.0x20 mm)

System 3

Linear gradient 5-100% CH₃CN in 8 min+1.8 min 100% CH₃CN (0.1% HCOOH); detection at 215 nm, flow rate 2 mL/min at 40 $^{\circ}$ C. Column: XERRA-MS (waters) 5 μ m C18 (50x4.6 mm)

System 4

Linear gradient 20-100% CH₃CN in 5 min+1 min 100% CH₃CN (0.1% TFA); detection at 215 nm, flow rate 1 mL/min at 30 $^{\circ}$ C. Column: Nucleosil 100-3 C18 (70x4.0 mm)

Abbreviations and Acronyms:

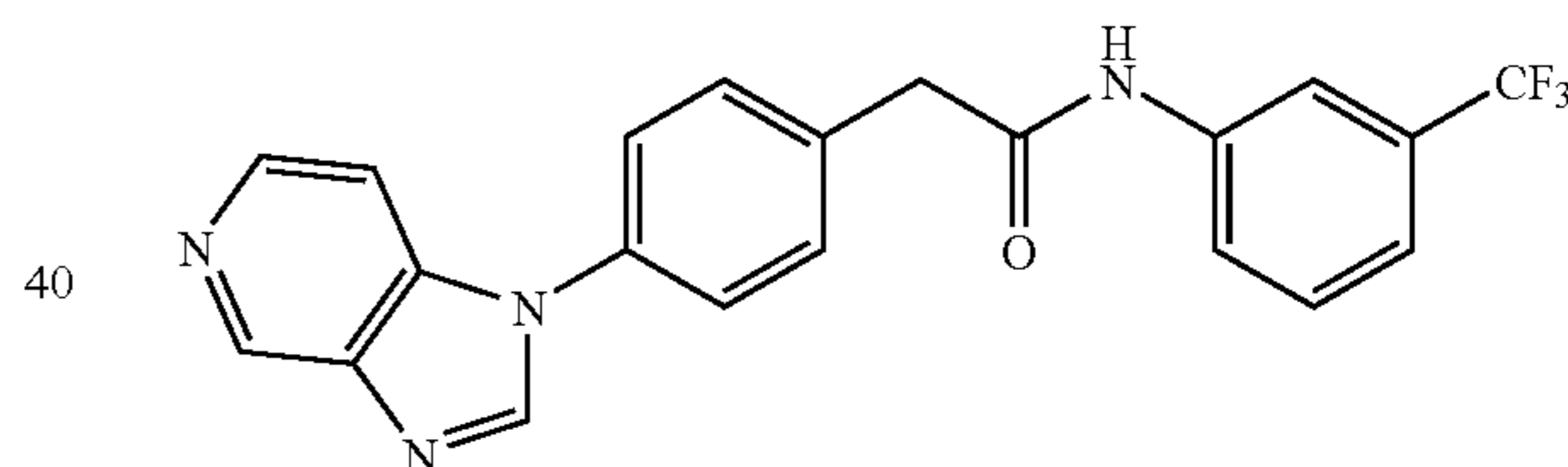
ACN	acetonitrile (CH ₃ CN)
AcOH	acetic acid
brine	saturated solution of NaCl in water
t-Bu ₃ P	tri-tert-butylphosphine
conc.	Concentrated
CuI	copper(I) iodide
DCM	dichloromethane (CH ₂ Cl ₂)
DIEA	Diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	N,N-dimethyl formamide
DMP	1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone
DMSO	N,N-dimethylsulfoxide
equiv	equivalent(s)
Et ₃ N	triethylamine
Et ₂ NH	diethylamine
Et ₂ O	diethylether
EtOAc	ethyl acetate
EtOH	ethanol
h	hour(s)
HPLC	high pressure liquid chromatography

-continued

L	liter(s)
Me	methyl
MeOH	methanol
5 ml	milliliter(s)
min	minute(s)
MPLC	medium pressure liquid chromatography
MS	mass spectrum
NMR	Nuclear Magnetic Resonance
NMP	1-methyl-2-pyrrolidone
10 PdCl ₂ (dppf) ₂	[1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II)
Pd(PhCN) ₂ Cl ₂	bis(benzonitrile)palladium(II) chloride
Pd(PPh ₃) ₄	tetrakis(triphenylphosphine)palladium(0)
Ph	phenyl
i-Pr ₂ NH	diisopropylamine
15 R _f	ratio of fronts (TLC)
rt	room temperature
TBTU	O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
20 TLC	thin layer chromatography
t _R	retention time (HPLC)
Trademarks	
Celite =	Celite [®] (The Celite Corporation) = filtering aid based on diatomaceous earth
25 Nucleosil =	Nucleosil [®] , trademark of Machery & Nagel, Düren, FRG for HPLC materials

Reference Example 0

2-(4-Imidazo[4,5-c]pyridin-1-yl-phenyl)-N-(3-trifluoromethyl-phenyl)-acetamide



0.15 ml of DIEA are added dropwise to a cold (0 $^{\circ}$ C.) mixture of 55 mg of crude (4-imidazo[4,5-c]pyridin-1-yl-phenyl)-acetic acid, 39 mg of 3-aminobenzotrifluoride and 77 mg of TBTU in 0.5 ml of DMF. The mixture obtained is allowed to warm to rt, stirred for 2 hours, diluted with EtOAc and washed with a saturated aqueous solution of NaHCO₃, H₂O, and brine. The organic phase obtained is dried (Na₂SO₄), filtered and concentrated in vacuo. The evaporation residue obtained is purified by silica gel column chromatography. 2-(4-Imidazo[4,5-c]pyridin-1-yl-phenyl)-N-(3-trifluoromethyl-phenyl)-acetamide is obtained in the form of a solid: ES-MS: 397.0 [M+H]⁺; single peak at t_R=3.52 min (System 1); R_f=0.18 (CH₂Cl₂/MeOH, 94:6).

Starting material is prepared as follows:

Step 0.1: (4-Imidazo[4,5-c]pyridin-1-yl-phenyl)-acetic acid

A mixture of 0.349 g of (4-imidazo[4,5-c]pyridin-1-yl-phenyl)-acetic acid methyl ester and 3.5 ml of an 6 N aqueous solution of HCl is stirred and refluxed for 3 hours. The mixture obtained is allowed to cool to rt and is concentrated in vacuo. (4-Imidazo[4,5-c]pyridin-1-yl-phenyl)-acetic acid in the form of a hydrochloric acid salt is obtained: ES-MS: 254.0 [M+H]⁺; single peak at t_R=1.20 min (System 1).

41

Step 0.2: (4-Imidazo[4,5-c]pyridin-1-yl-phenyl)-acetic acid methyl ester

A mixture of 0.356 g of [4-(3-amino-pyridin-4-ylamino)-phenyl]-acetic acid methyl ester and 9.2 ml of triethyl orthoformate is stirred and refluxed for 2 hours. The mixture obtained is allowed to cool to rt and is concentrated in vacuo. (4-Imidazo[4,5-c]pyridin-1-yl-phenyl)-acetic acid methyl ester is obtained in the form of a solid: ES-MS: 268.1 [M+H]⁺; single peak at t_R=2.03 min (System 1).

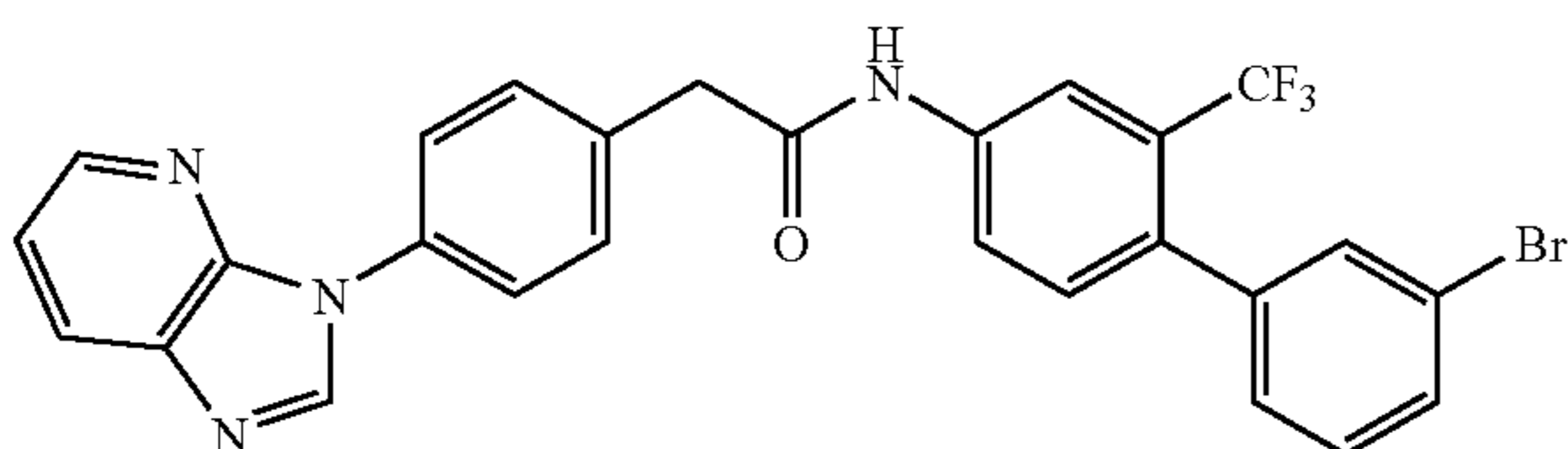
Step 0.3: [4-(3-Amino-pyridin-4-ylamino)-phenyl]-acetic acid methyl ester

A mixture of 0.500 g of 4-chloro-3-nitro-pyridine (LANCASTER) and 0.467 g of (4-amino-phenyl)-acetic acid (Aldrich) in 10 ml of MeOH/dioxane (1/1 v/v) is stirred and refluxed for 6 hours. The mixture obtained is allowed to cool to rt and is concentrated in vacuo. Crude [4-(3-nitro-pyridin-4-ylamino)-phenyl]-acetic acid methyl ester is obtained.

0.569 g of a suspension of crude [4-(3-nitro-pyridin-4-ylamino)-phenyl]acetic acid methyl ester and 0.140 g of Raney Ni in 15 ml of MeOH is stirred for 21 hours at rt under a hydrogen atmosphere. The mixture obtained is filtered through a pad of Celite and the filtrate obtained is concentrated. The concentration residue obtained is triturated in CH₂Cl₂. [4-(3-Amino-pyridin-4-ylamino)-phenyl]-acetic acid methyl ester is obtained in the form of a solid: ES-MS: 258.0 [M+H]⁺; single peak at t_R=2.54 min (System 1).

Reference Example 1

N-(3'-Bromo-2-trifluoromethyl-biphen-4-yl)-2-(4-imidazo[4,5-b]pyridin-3-yl-phenyl)-acetamide



is obtained analogously to the method as described in Reference Example 0 but using 3'-bromo-2-trifluoromethyl-biphen-4-ylamine instead of 3-aminobenzotrifluoride and (4-imidazo[4,5-b]pyridin-3-yl-phenyl)-acetic acid instead of (4-imidazo[4,5-c]pyridin-1-yl-phenyl)-acetic acid as a starting material. ES-MS: 552.8 [M+H]⁺; t_R=5.24 min (System 1); R_f=0.20 (CH₂Cl₂/MeOH, 96:4).

Starting material is prepared as follows:

Step 1.1: (4-Imidazo[4,5-b]pyridin-3-yl-phenyl)-acetic acid Procedure A

Analogously to the method as described in Step 0.1 but using (4-imidazo[4,5-b]pyridin-3-yl-phenyl)-acetic acid methyl ester instead of (4-imidazo[4,5-c]pyridin-1-yl-phenyl)-acetic acid methyl ester as a starting material, (4-imidazo[4,5-b]pyridin-3-yl-phenyl)-acetic acid is obtained. ES-MS: 254.0 [M+H]⁺; t_R=2.35 min (System 1).

Procedure B

A mixture of 400 mg of 4-iodophenylacetic acid, 273 mg of 4-azabenzimidazole, 17.9 mg of trans,trans-dibenzylideneacetone, 303 mg of 1,10-phenanthroline, 19.2 mg of copper (I) trifluoromethanesulfonate benzene complex and 547 mg of Cs₂CO₃ in 1.5 ml of xylene is stirred for 80 hours at 125° C. The mixture obtained is allowed to cool to rt and concentrated in vacuo. The concentration residue obtained is dissolved in aqueous 1N NaOH solution and extracted with

42

EtOAc. To the aqueous layer aqueous 1N HCl is added in order to obtain an acidic pH and the mixture obtained is extracted with CH₂Cl₂. The organic phase obtained is dried (Na₂SO₄), filtered and concentrated. The concentration residue obtained is subjected to reversed phase MPLC(CH₃CN/H₂O/TFA). (4-Imidazo[4,5-b]pyridin-3-yl-phenyl)-acetic acid is obtained.

Step 1.2: (4-Imidazo[4,5-b]pyridin-3-yl-phenyl)-acetic acid methyl ester

is obtained analogously to the method as described in Step 0.2 but using [4-(3-amino-pyridin-2-ylamino)-phenyl]-acetic acid methyl ester instead of [4-(3-amino-pyridin-4-ylamino)-phenyl]-acetic acid methyl ester as a starting material. ES-MS: 268.0 [M+H]⁺; t_R=3.20 min (System 1).

Step 1.3: [4-(3-Amino-pyridin-2-ylamino)-phenyl]-acetic acid methyl ester

2 g of a suspension of [4-(3-nitro-pyridin-2-ylamino)-phenyl]-acetic acid methyl ester and 0.600 g of Raney Ni in 40 ml of MeOH (40 mL) is stirred for 4 hours at rt under a hydrogen atmosphere. The mixture obtained is filtered through a pad of Celite and concentrated. [4-(3-Amino-pyridin-2-ylamino)-phenyl]-acetic acid methyl ester is obtained in the form of a solid: ES-MS: 258.0 [M+H]⁺; t_R=2.30 min (System 1); R_f=0.15 (Hexane/EtOAc, 1:1).

Step 1.4: [4-(3-Nitro-pyridin-2-ylamino)-phenyl]-acetic acid methyl ester

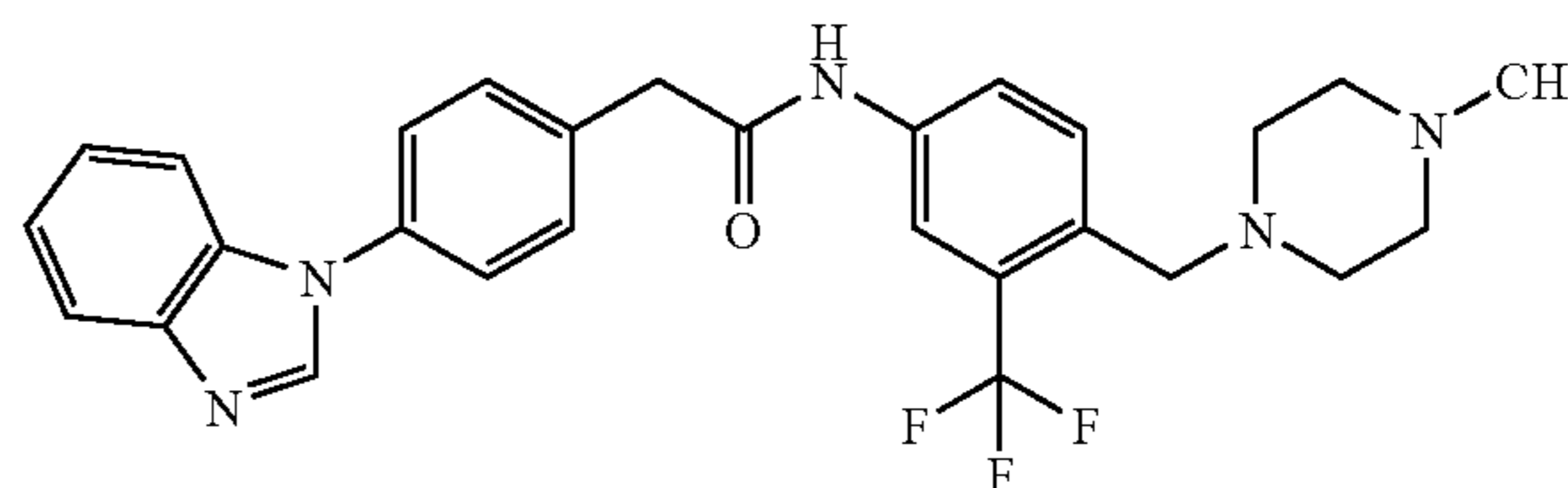
A mixture of 5.0 g of 2-chloro-3-nitro-pyridine, 4.75 g of (4-amino-phenyl)-acetic acid and a 4 N solution of HCl in 7.85 ml dioxane in 100 ml of MeOH/dioxane (1:1, v/v) is stirred and refluxed for 30 hours. To the mixture obtained 4.75 g of (4-amino-phenyl)-acetic acid are added and the mixture obtained is stirred and refluxed for 18 hours. The mixture obtained is allowed to cool to rt and is concentrated in vacuo. The concentration residue obtained is dissolved in EtOAc, the mixture obtained is washed with a saturated aqueous solution of NaHCO₃, dried (Na₂SO₄), filtered and concentrated. The concentration residue obtained is subjected to silica gel column chromatography. [4-(3-Nitro-pyridin-2-ylamino)-phenyl]-acetic acid methyl ester is obtained in the form of a solid: ES-MS: 288.0 [M+H]⁺; t_R=4.71 min (System 1); R_f=0.20 (Hexane/EtOAc, 4:1).

Step 1.5: 3'-Bromo-2-trifluoromethyl-biphenyl-4-amine

A mixture of 500 mg of 5-amino-2-bromobenzotrifluoride (Dakwood Products, Inc.), 6.2 mMol 3-bromophenylboronic acid (Aldrich), 70 mg of Pd(PPh₃)₄ and 5 ml of Na₂CO₃, 2 M solution in H₂O, in 14 ml of toluene is stirred at reflux for 1 hour. The mixture obtained is allowed to cool to rt and filtered through a pad of celite. The layers obtained are separated and the aqueous phase obtained is extracted with CH₂Cl₂. The organic phase obtained is washed with brine, dried (Na₂SO₄), filtered and concentrated in vacuo. The concentration residue obtained is subjected to MPLC(CH₃CN/H₂O/TFA). 3'-Bromo-2-trifluoromethyl-biphenyl-4-amine is obtained. MS: 315.9 [M-1]⁻; HPLC^Dt_{Ret}=4.9; R_f=0.16 (Hexane/EtOAc, 4:1).

Reference Example 2

2-(4-Benzoimidazol-1-yl-phenyl)-N-[4-(4-methyl-piperazin-1-ylmethyl)-3-trifluoromethyl-phenyl]-acetamide



43

is obtained analogously to the method as described in Example 1 but using (4-benzimidazol-1-yl-phenyl)-acetic acid instead of (4-imidazo[4,5-b]pyridin-3-yl-phenyl)-acetic acid and 4-(4-methyl-piperazin-1-ylmethyl)-3-trifluoromethyl-phenylamine instead of 3'-bromo-2-trifluoromethyl-biphen-4-ylamine as a starting material (see WO 03/099771). ES-MS: 508.0 [M+H]⁺; single peak at $t_R=2.84$ min (System 1); $R_f=0.10$ (CH₂Cl₂/MeOH+1% NH₃^{aq}, 9:1).

Starting material is prepared as follows:

Step 2.1: (4-Benzimidazol-1-yl-phenyl)-acetic acid

Procedure A

(4-Benzimidazol-1-yl-phenyl)-acetic acid is obtained analogously to the method as described in Step 1.1, but using (4-benzimidazol-1-yl-phenyl)-acetic acid methyl ester instead of 4-imidazo[4,5-b]pyridin-3-yl-phenyl)-acetic acid methyl ester as a starting material. ES-MS: 253.1 [M+H]⁺; single peak at $t_R=2.36$ min (System 1).

Procedure B

A mixture of 0.535 g of (4-benzimidazol-1-yl-phenyl)-acetic acid methyl ester and 2 ml of an 1N aqueous solution of LiOH in 2 ml of THF is stirred for 3 hours at 45° C. The mixture obtained is allowed to cool to rt and acidified to pH 5 by addition of 0.5 N aqueous HCl. A solid precipitates and is collected by vacuum filtration. (4-Benzimidazol-1-yl-phenyl)-acetic acid is obtained. ES-MS: 253.1 [M+H]⁺; single peak at $t_R=2.36$ min (System 1).

Procedure C

A mixture of 4.4 g of 4-iodophenylacetic acid, 2.98 g of benzimidazole, 197 mg of trans,trans-dibenzylideneacetone, 3.33 g of 1,10-phenanthroline, 211 mg of copper (I) trifluoromethanesulfonate benzene complex and 6 g of Cs₂CO₃ in 12 ml of xylene is stirred for 88 hours at 125° C. The mixture obtained is allowed to cool to rt and concentrated in vacuo. The concentration residue obtained is dissolved in 1N NaOH aqueous solution and the mixture obtained is extracted with EtOAc. The pH of the aqueous layer obtained is adjusted to acidic pH by addition of 1N HCl aqueous solution. A precipitate forms and is collected by vacuum filtration (batch 1) is collected by vacuum filtration. The aqueous phase from the filtrate obtained is extracted with CH₂Cl₂. The organic phase is dried (Na₂SO₄), filtered and concentrated. The concentration residue obtained (batch 2) is combined with batch 1 and triturated in Et₂O. 3.58 g of (4-benzimidazol-1-yl-phenyl)-acetic acid are obtained.

Step 2.2: (4-Benzimidazol-1-yl-phenyl)-acetic acid methyl ester

is obtained analogously to the method as described in Step 1.2 but using [4-(2-amino-phenylamino)-phenyl]-acetic acid methyl ester instead of 4-(3-amino-pyridin-2-ylamino)-phenyl]-acetic acid methyl ester as a starting material. ES-MS: 267.1 [M+H]⁺; single peak at $t_R=3.00$ min (System 1).

Step 2.3: [4-(2-Amino-phenylamino)-phenyl]-acetic acid methyl ester

0.700 g of a suspension of [4-(2-nitro-phenylamino)-phenyl]-acetic acid methyl ester and 0.240 g of Pd/C (10%) in 20 ml of MeOH is stirred for 3 hours at rt under a hydrogen atmosphere. The mixture obtained is filtered through a pad of Celite and the filtrate obtained is concentrated. [4-(2-Amino-phenylamino)-phenyl]-acetic acid methyl ester is obtained in the form of an oil: ES-MS: 257.1 [M+H]⁺; single peak at $t_R=3.04$ min (System 1).

Step 2.4: [4-(2-Nitro-phenylamino)-phenyl]-acetic acid methyl ester

A mixture of 1.0 g of [4-(2-nitro-phenylamino)-phenyl]-acetic acid and 0.4 ml of HCl conc. in 20 ml of MeOH is stirred and refluxed for 1 hour. The mixture obtained is allowed to cool to rt, and is concentrated in vacuo. The con-

44

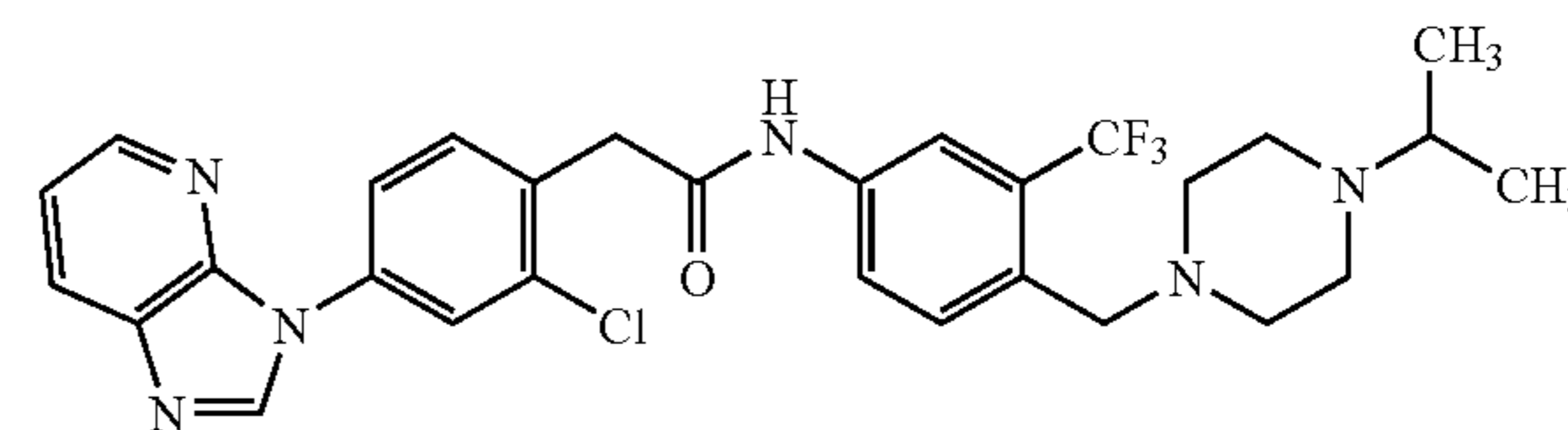
centrate obtained is diluted with CH₂Cl₂, the mixture obtained is washed with an aqueous saturated solution of NaHCO₃, H₂O, and brine, dried (Na₂SO₄), filtered and concentrated. The concentrate obtained is subjected to silica gel column chromatography. [4-(2-Nitro-phenylamino)-phenyl]-acetic acid methyl ester is obtained in the form of an oil: ES-MS: 287.0 [M+H]⁺; single peak at $t_R=5.01$ min (System 1); $R_f=0.20$ (Hexane/EtOAc, 4:1).

Step 2.5: [4-(2-Nitro-phenylamino)-phenyl]-acetic acid

A mixture of 1.5 ml of 2-nitrofluorobenzene (Aldrich), 1.44 g of 4-aminophenyl acetic acid and 0.550 g of KF is stirred at 170° C. for 16 hours in a sealed tube. The mixture obtained is allowed to cool to rt, triturated in CH₂Cl₂/MeOH (95:5) and filtered. The filtrate obtained is concentrated and the concentrate obtained is purified by silica gel column chromatography. [4-(2-Nitro-phenylamino)-phenyl]-acetic acid is obtained in the form of a solid: ES-MS: 273.0 [M+H]⁺; single peak at $t_R=4.44$ min (System 1); $R_f=0.20$ (CH₂Cl₂/MeOH, 95:5).

Reference Example 3

2-(2-Chloro-4-imidazo[4,5-b]pyridin-3-yl-phenyl)-N-[4-(4-isopropyl-piperazin-1-ylmethyl)-3-trifluoromethyl-phenyl]-acetamide



is obtained analogously to the method as described in Example 1 but using (2-chloro-4-imidazo[4,5-b]pyridin-3-yl-phenyl)-acetic acid instead of (4-imidazo[4,5-b]pyridin-3-yl-phenyl)-acetic acid and 4-(4-isopropyl-piperazin-1-ylmethyl)-3-trifluoromethyl-phenylamine instead of 3'-bromo-2-trifluoromethyl-biphen-4-ylamine (see WO 03/099771). ES-MS: 570.9 [M+H]⁺; single peak at $t_R=3.46$ min (System 1); $R_f=0.26$ (CH₂Cl₂/MeOH+1% NH₃^{aq}, 9:1).

Starting material is prepared as follows:

Step 3.1: (2-Chloro-4-imidazo[4,5-b]pyridin-3-yl-phenyl)-acetic acid

A mixture of 0.325 g (2-chloro-4-imidazo[4,5-b]pyridin-3-yl-phenyl)-acetic acid ethyl ester and 2 ml of 0.5 N aqueous solution of LiOH in 2 ml of THF is stirred for 1 hour at 40 C. The mixture obtained is allowed to cool to rt and an acidic pH is adjusted by addition of 0.5 N HCl aqueous solution. A precipitate forms and is collected by vacuum filtration. (2-Chloro-4-imidazo[4,5-b]pyridin-3-yl-phenyl)-acetic acid is obtained in the form of a solid. ES-MS: 288.0 [M+H]⁺; single peak at $t_R=3.00$ min (System 1).

Step 3.2: (2-Chloro-4-imidazo[4,5-b]pyridin-3-yl-phenyl)-acetic acid ethyl ester

is obtained analogously to the method as described in Step 1.2 but using [4-(3-amino-pyridin-2-ylamino)-2-chloro-phenyl]-acetic acid ethyl ester instead of [4-(3-amino-pyridin-2-ylamino)-phenyl]-acetic acid methyl ester as a starting material. ES-MS: 316.1 [M+H]⁺; single peak at $t_R=4.24$ min (System 1); $R_f=0.16$ (Hexane/EtOAc, 1:1).

45

Step 3.3: [4-(3-Amino-pyridin-2-ylamino)-2-chloro-phenyl]-acetic acid ethyl ester

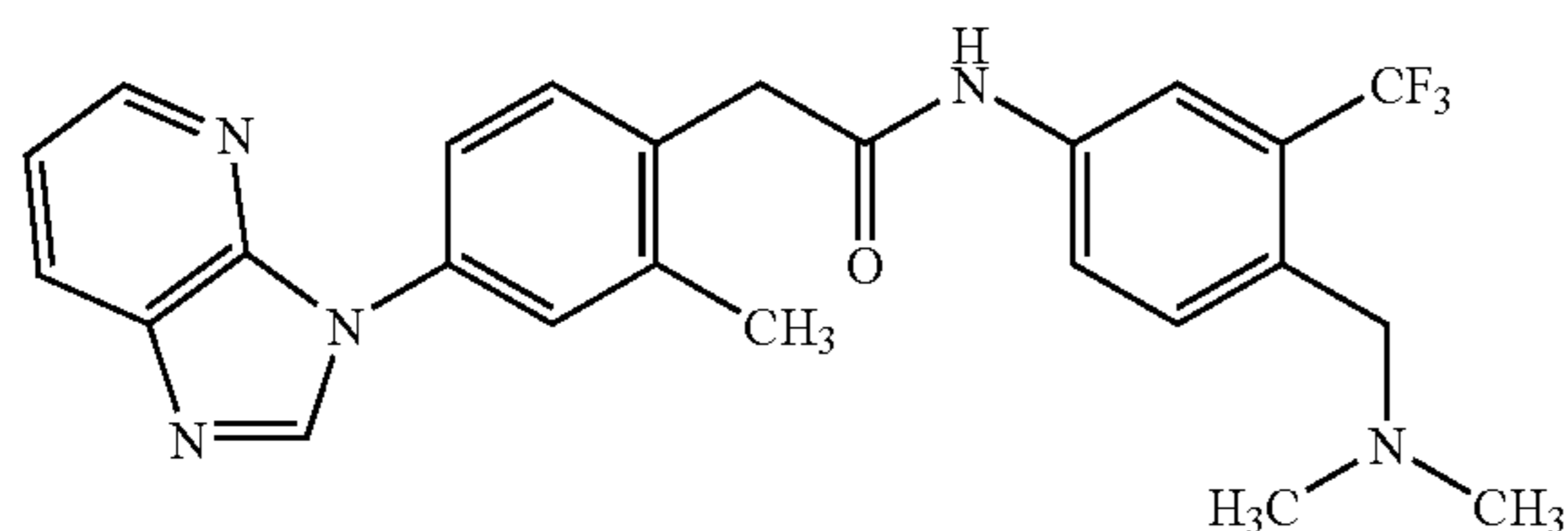
is obtained analogously to the method as described in Step 1.3 but using [2-chloro-4-(3-nitro-pyridin-2-ylamino)-phenyl]-acetic acid ethyl ester instead of [4-(3-nitro-pyridin-2-ylamino)-phenyl]-acetic acid methyl ester as a starting material, EtOH instead of MeOH as the solvent and the reaction mixture is stirred for 22 hours instead of 4 hours at rt. ES-MS: 306.1 [M+H]⁺; single peak at t_R=3.06 min (System 1); R_f=0.16 (Hexane/EtOAc, 1:1).

Step 3.4: [2-Chloro-4-(3-nitro-pyridin-2-ylamino)-phenyl]-acetic acid ethyl ester

A mixture of 0.600 g of 2-chloro-3-nitro-pyridine (Aldrich) and 0.800 g of (4-amino-2-chloro-phenyl)-acetic acid ethyl ester (see WO 97/21665) in 20 ml of EtOH/dioxane (1:1, v/v) is stirred and refluxed for 72 hours. The mixture obtained is allowed to cool to rt and is concentrated in vacuo. The concentrate obtained is subjected to silica gel column chromatography. A solid is obtained which is triturated with Et₂O. [2-Chloro-4-(3-nitro-pyridin-2-ylamino)-phenyl]-acetic acid ethyl ester is obtained in the form of a solid. ES-MS: 336.0 [M+H]⁺; single peak at t_R=5.59 min (System 1); R_f=0.39 (Hexane/EtOAc, 7:3).

Reference Example 4

N-(4-Diethylaminomethyl-3-trifluoromethyl-phenyl)-2-(4-imidazo[4,5-b]pyridin-3-yl-2-methyl-phenyl)-acetamide



is obtained analogously to the method as described in Reference Example 1 but using (4-imidazo[4,5-b]pyridin-3-yl-2-methyl-phenyl)-acetic acid instead of (4-imidazo[4,5-b]pyridin-3-yl-phenyl)-acetic acid and 4-diethylaminomethyl-3-trifluoromethyl-phenylamine (disclosed in WO2005/051366) instead of 3'-bromo-2-trifluoromethyl-biphen-4-ylamine as a starting material. ES-MS: 496.0 [M+H]⁺; t_R=3.31 min (System 1); R_f=0.43 (CH₂Cl₂/MeOH, 95:5+0.1% NH₃^{aq}).

46

Step 4.1: (4-Imidazo[4,5-b]pyridin-3-yl-2-methyl-phenyl)-acetic acid

is obtained analogously to the method as described in Reference example 2, step 2.1, procedure B, but using (4-imidazo[4,5-b]pyridin-3-yl-2-methyl-phenyl)-acetic acid methyl ester instead of (4-benzoimidazol-1-yl-phenyl)-acetic acid methyl ester. ES-MS: 268.1 [M+H]⁺; t_R=2.59 min (System 1).

Step 4.2: (4-Imidazo[4,5-b]pyridin-3-yl-2-methyl-phenyl)-acetic acid methyl ester

A mixture of 1.92 g of [4-(3-amino-pyridin-2-ylamino)-2-methyl-phenyl]-acetic acid methyl ester and 30 ml of triethyl orthoformate is stirred for 3 hours at 150° C. The mixture obtained is allowed to cool to rt and concentrated in vacuo. 4-Imidazo[4,5-b]pyridin-3-yl-2-methyl-phenyl)-acetic acid methyl ester is obtained. ES-MS: 282.1 [M+H]⁺; t_R=3.39 min (System 1).

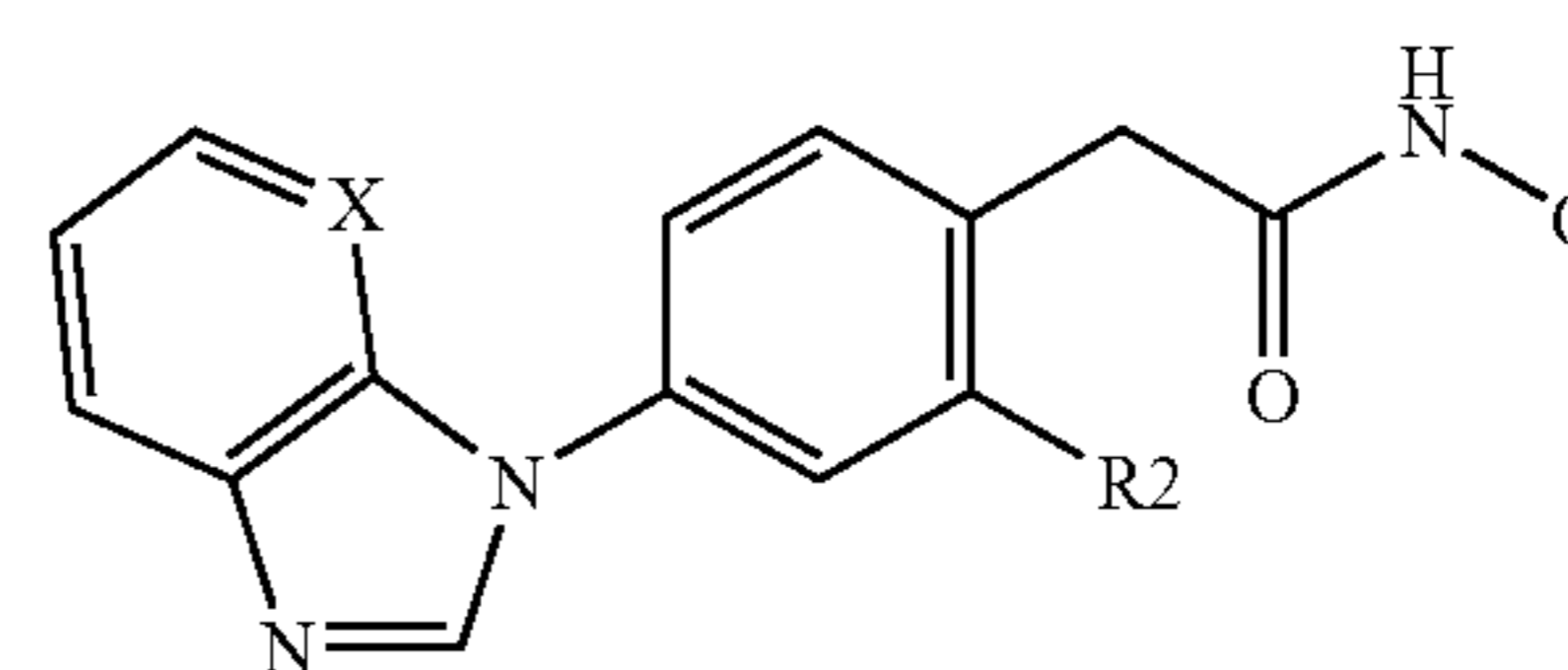
Step 4.3: [4-(3-Amino-pyridin-2-ylamino)-2-methyl-phenyl]-acetic acid methyl ester

A suspension of 2.2 g of [2-methyl-4-(3-nitro-pyridin-2-ylamino)-phenyl]-acetic acid methyl ester and 220 mg of Raney Ni is stirred for 6.5 hours at rt under a hydrogen atmosphere. The mixture obtained is filtered through a pad of celite and concentrated. [4-(3-Amino-pyridin-2-ylamino)-2-methyl-phenyl]-acetic acid methyl ester is obtained. ES-MS: 272.1 [M+H]⁺; t_R=2.53 min (System 1).

Step 4.4: [2-Methyl-4-(3-nitro-pyridin-2-ylamino)-phenyl]-acetic acid methyl ester

A mixture of 1.5 g of 2-chloro-3-nitro-pyridine, 3.39 g of (4-amino-2-methyl-phenyl)-acetic acid methyl ester and 6.9 ml of an 4 N solution of HCl in dioxane in 30 ml of MeOH/dioxane (1:1, v/v) is stirred for 54 hours at 100° C. The mixture obtained is allowed to cool to rt and concentrated in vacuo. The concentrate obtained is dissolved in EtOAc, the mixture obtained is washed with a saturated aqueous solution of NaHCO₃, dried (Na₂SO₄), filtered and concentrated. The concentrate obtained is subjected to silica gel column chromatography. [2-Methyl-4-(3-nitro-pyridin-2-ylamino)-phenyl]-acetic acid methyl ester is obtained. ES-MS: 302.1 [M+H]⁺; t_R=4.79 min (System 1); R_f=0.43 (CH₂Cl₂).

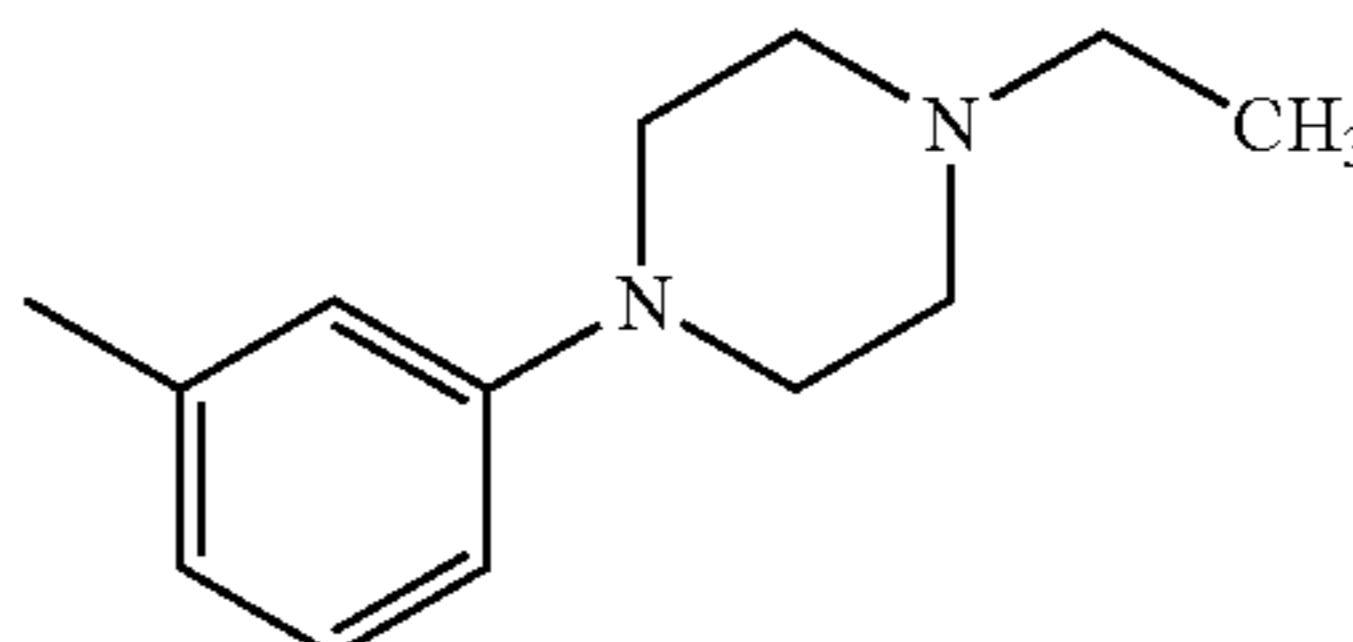
Analogously to a method as described in the Reference examples but using appropriate starting materials compounds of formula



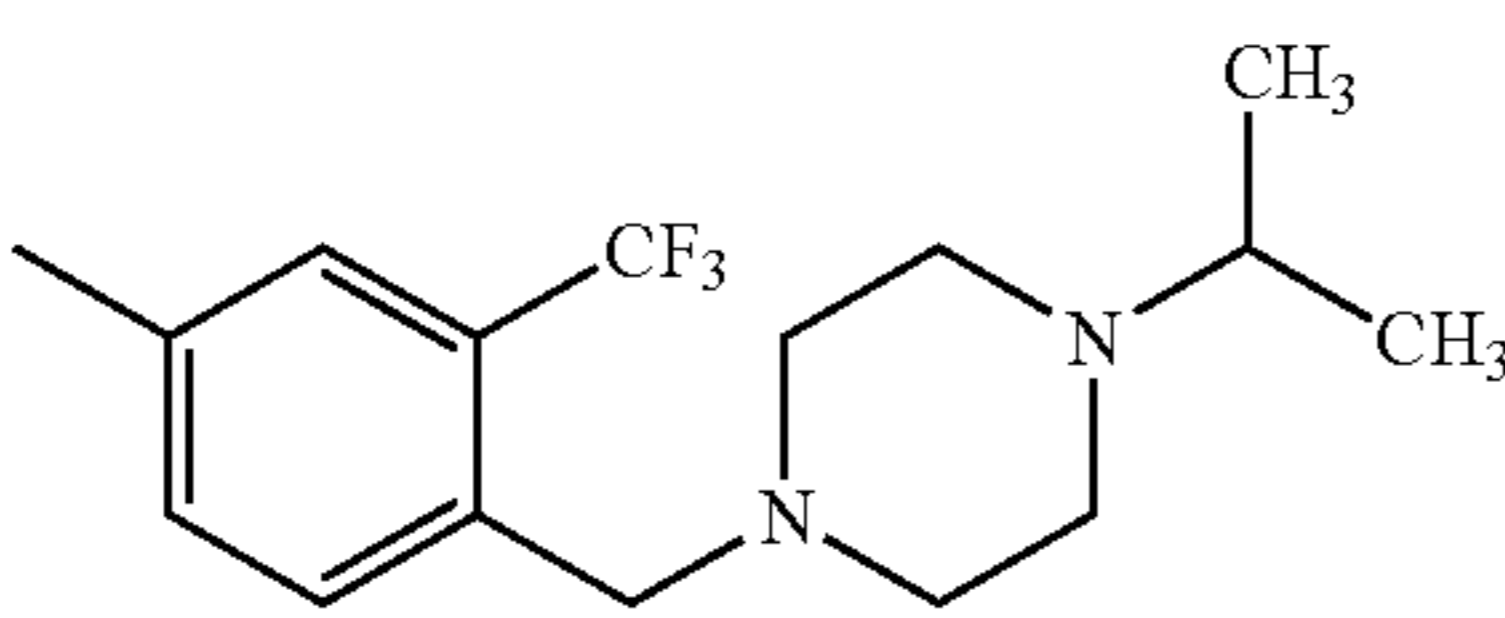
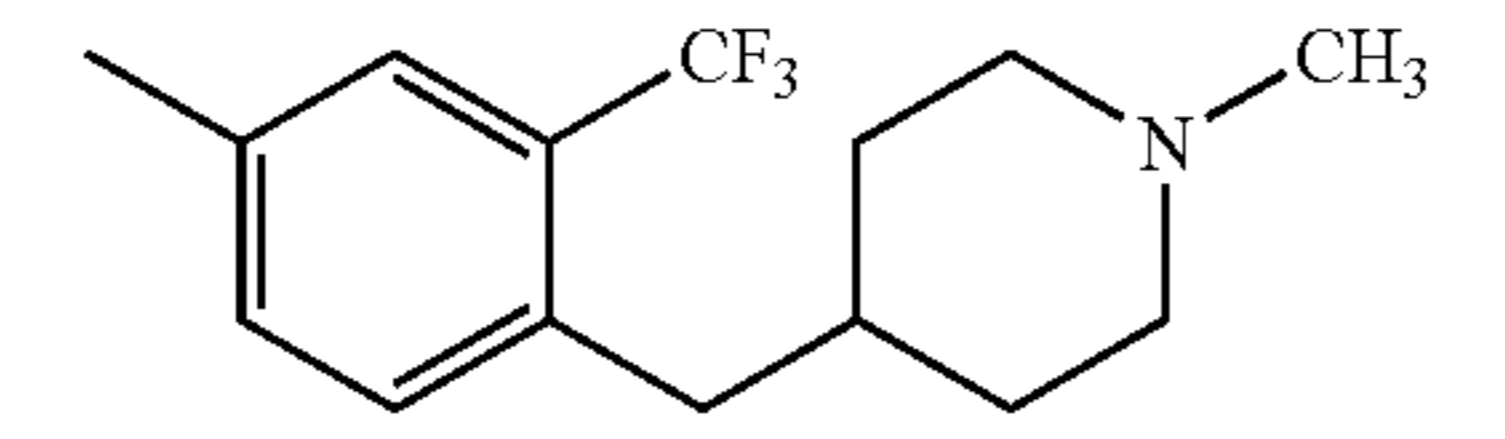
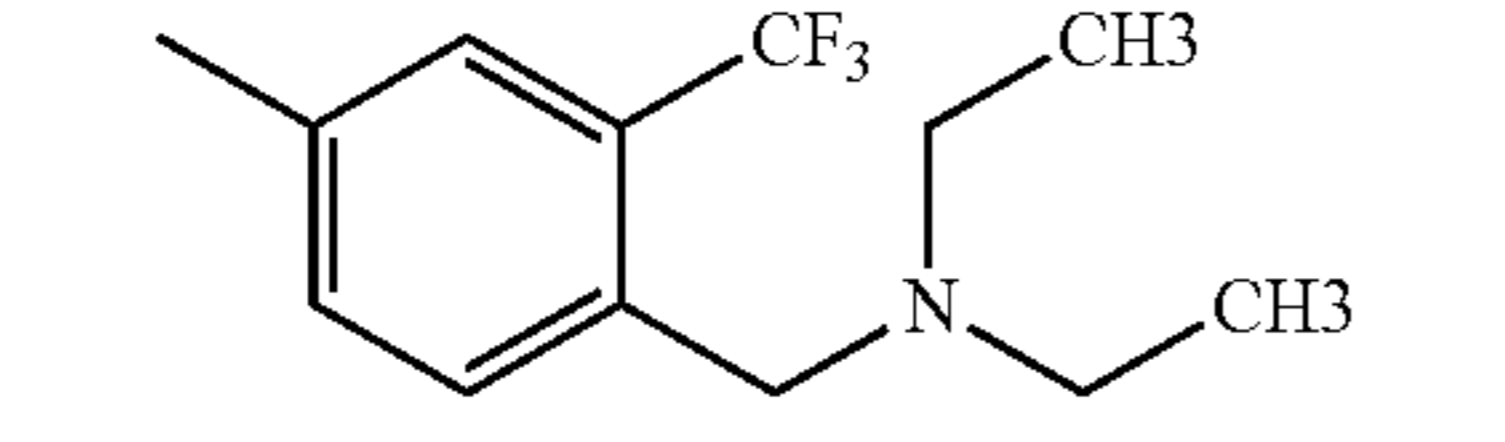
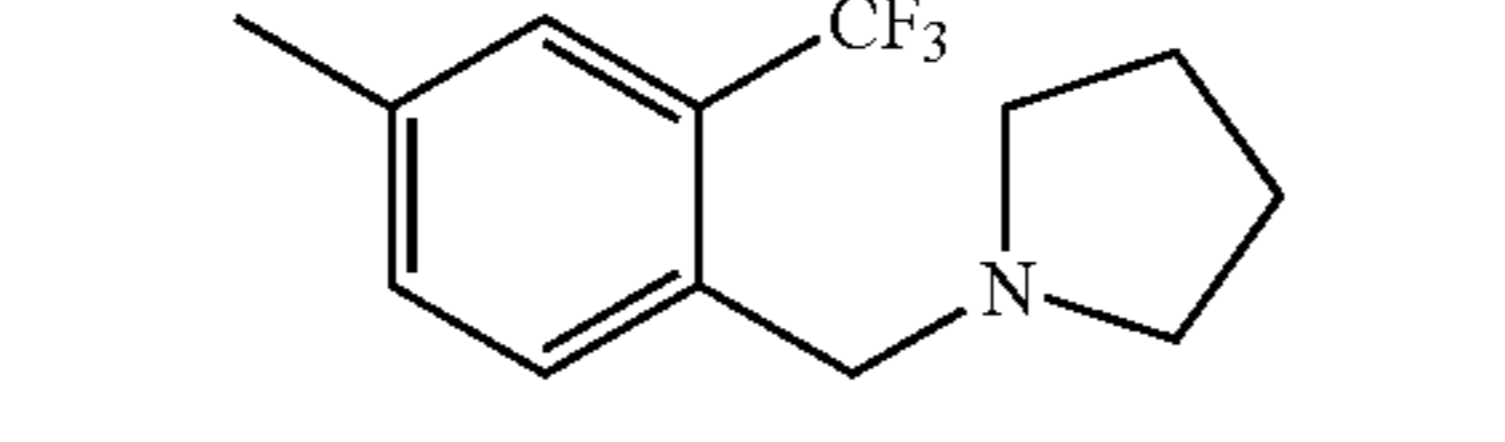
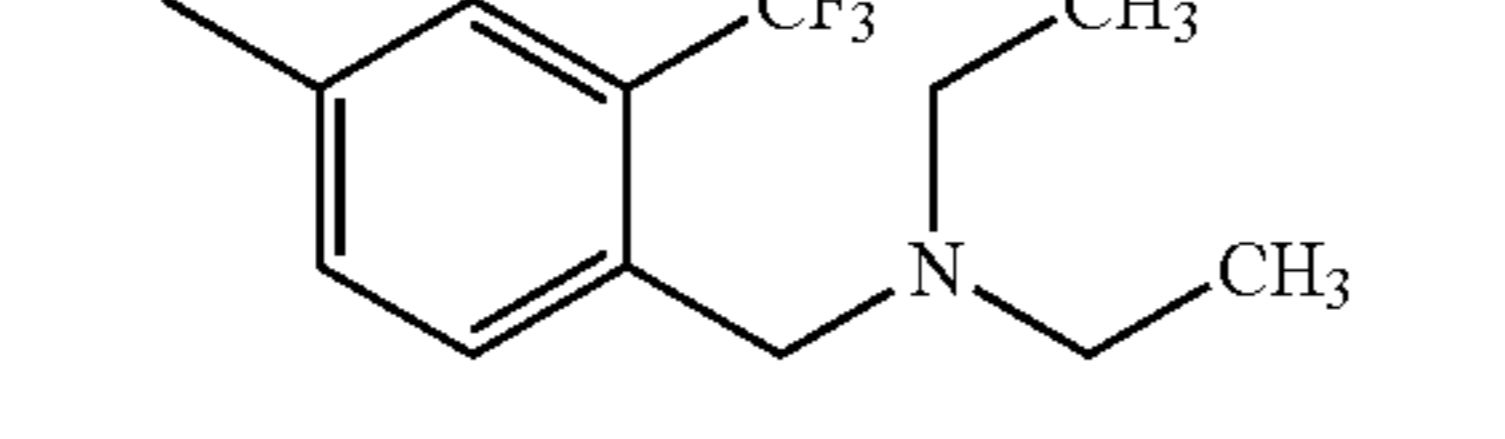
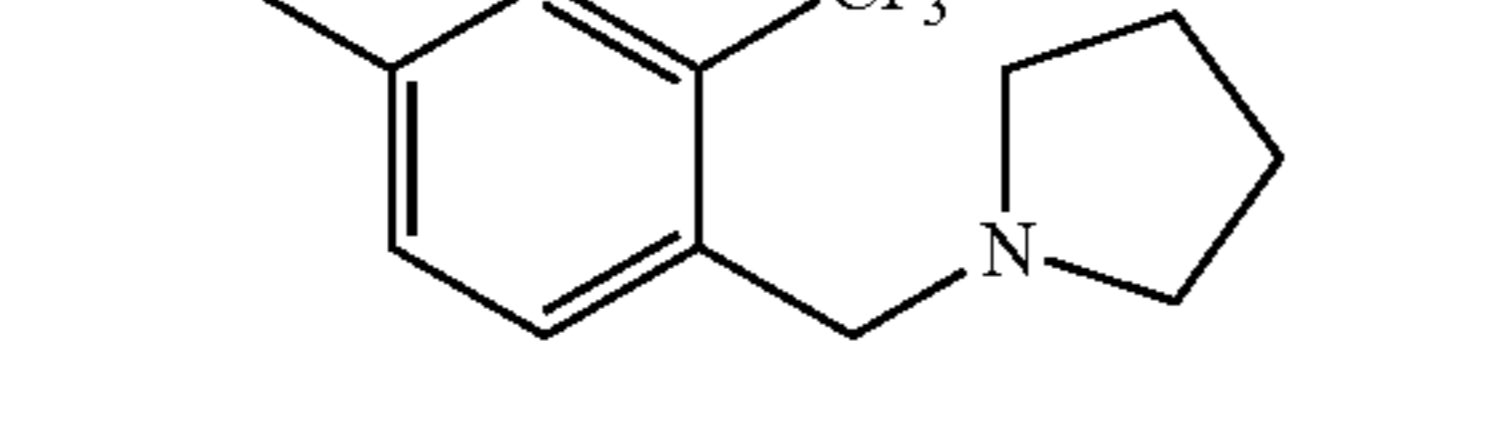
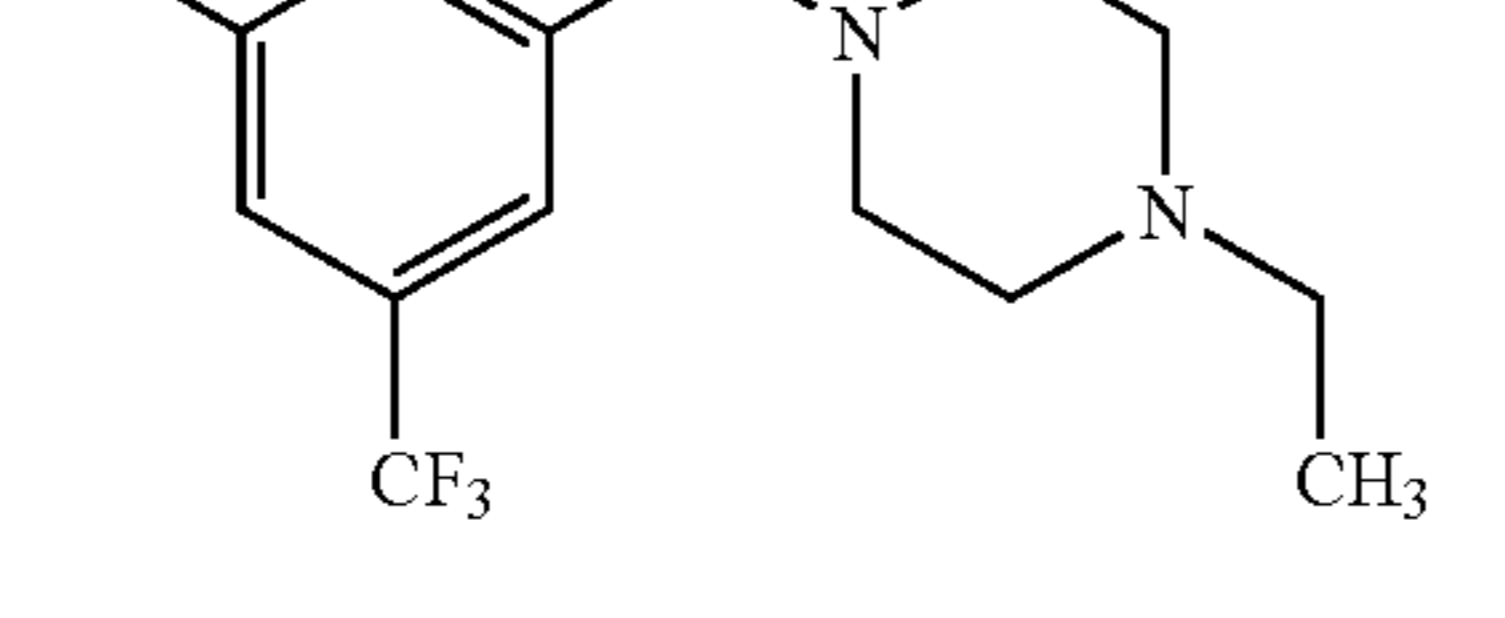
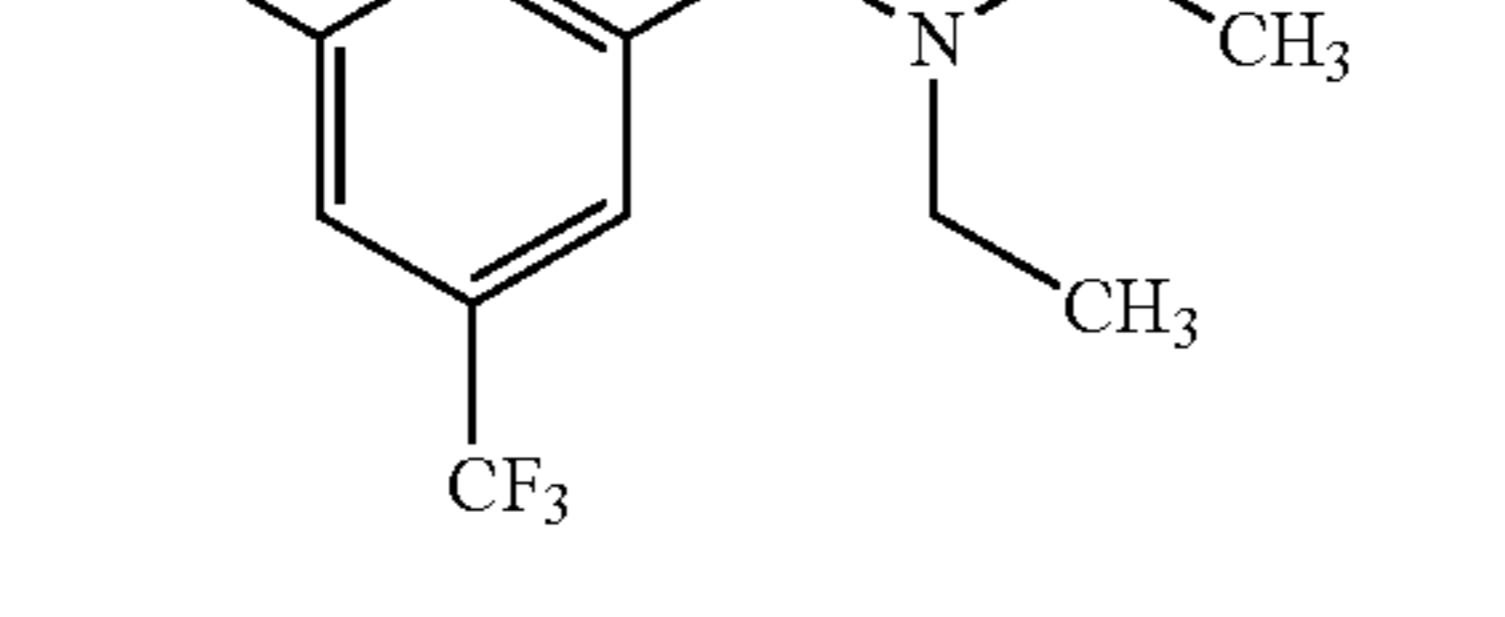
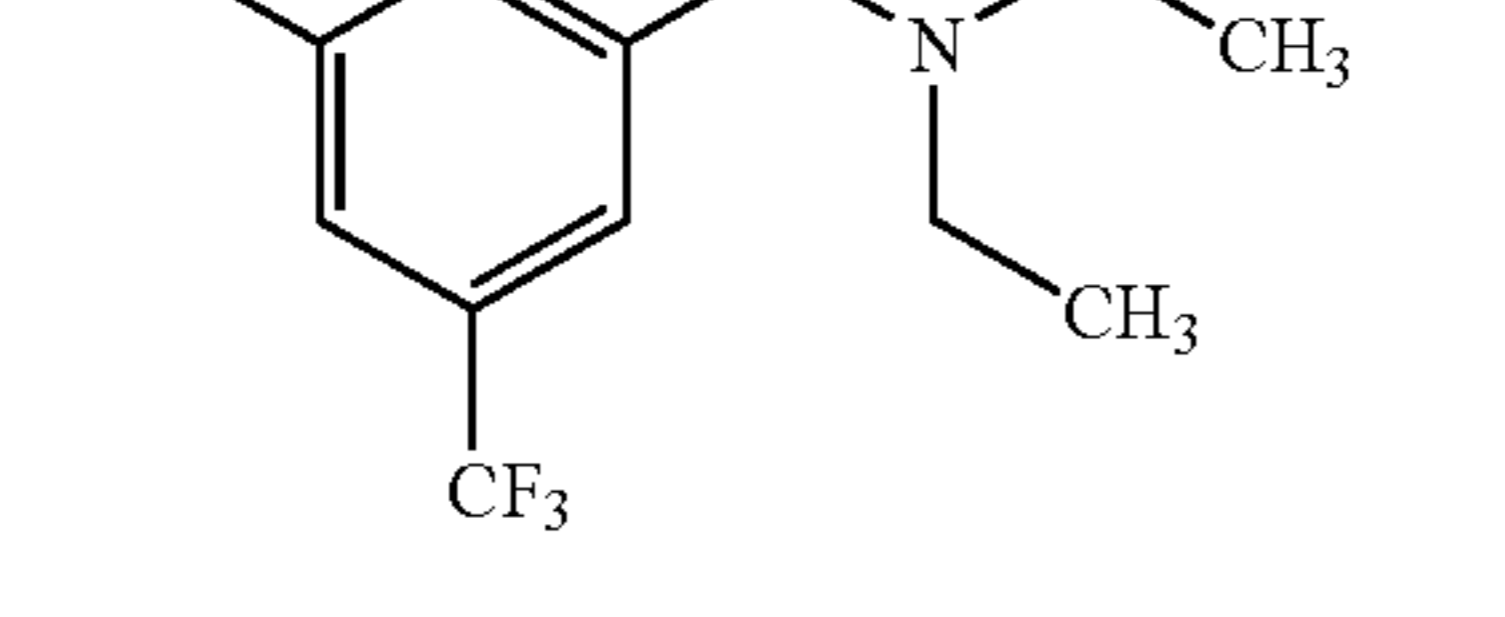
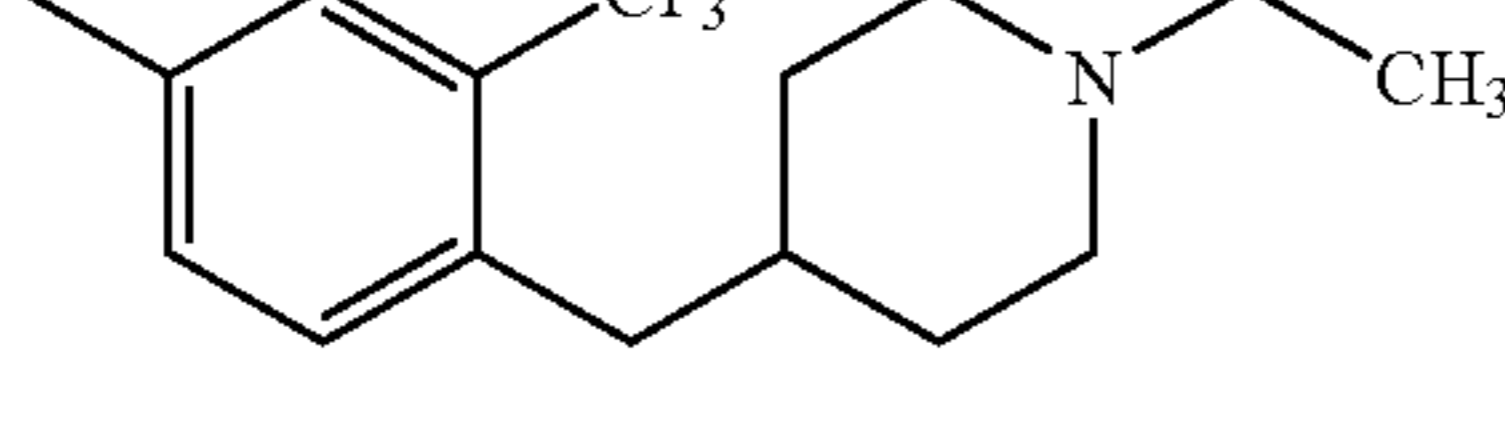
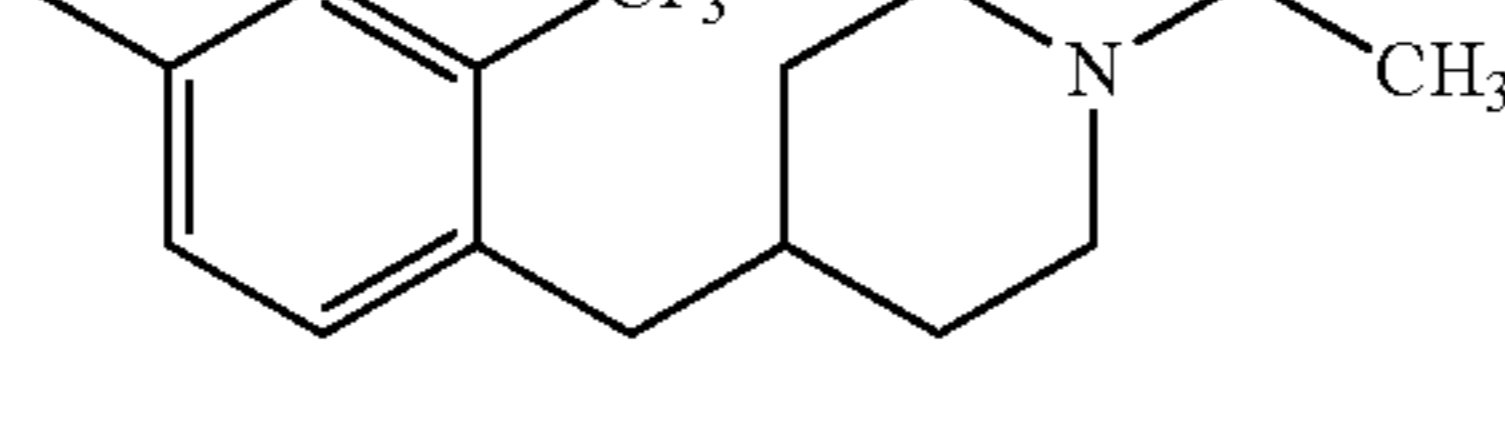
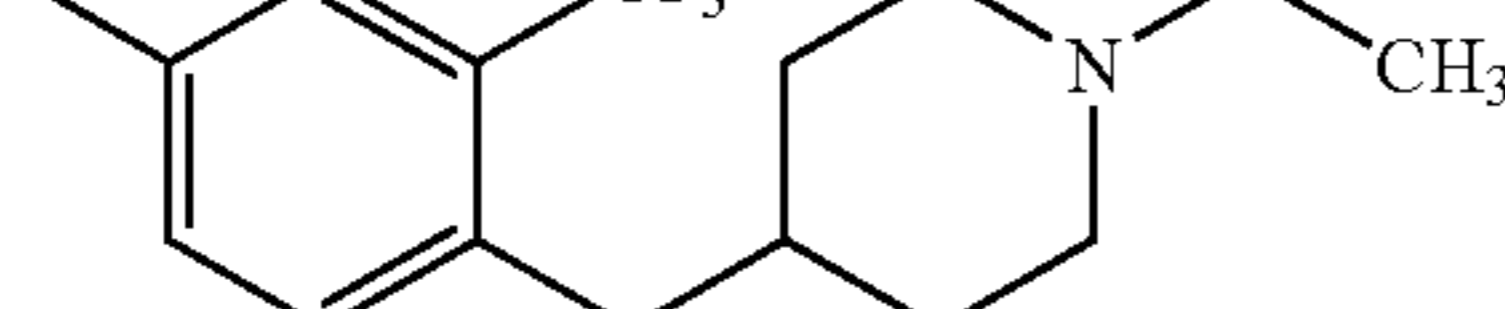
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are obtained wherein X, R₂ and Q are as defined in TABLE 1 below. Analytical data is also set out in TABLE 1.

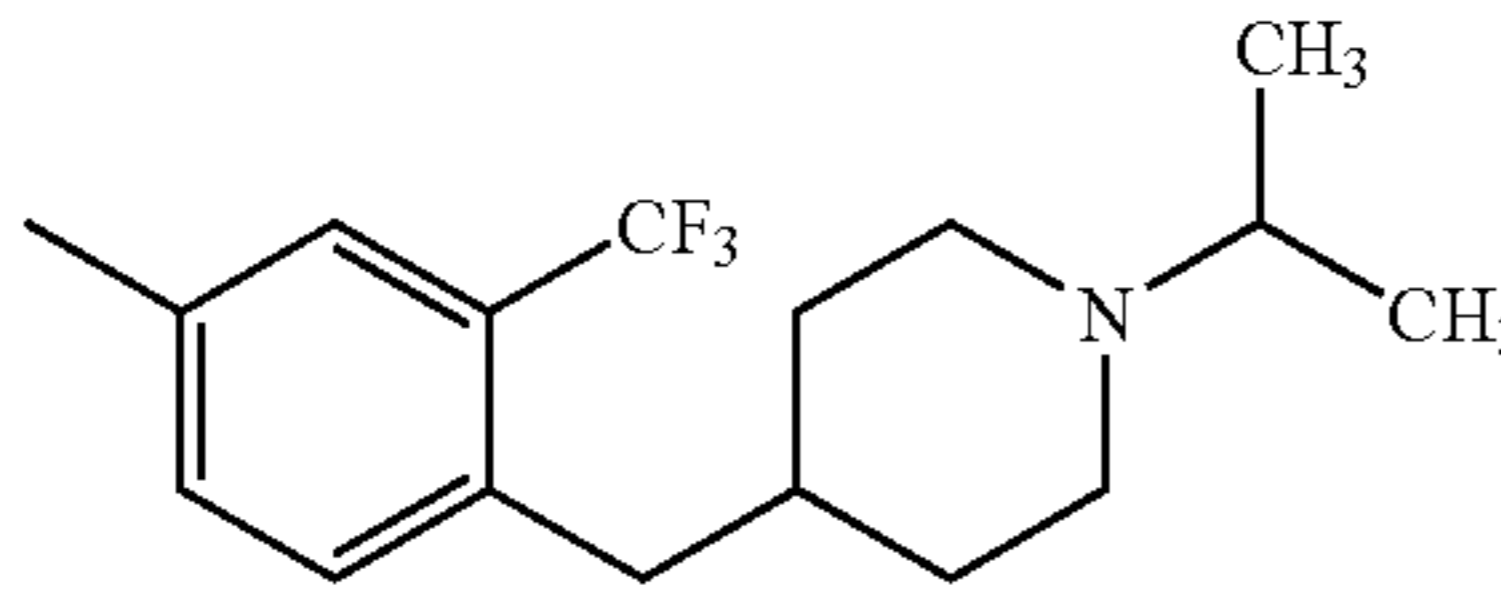
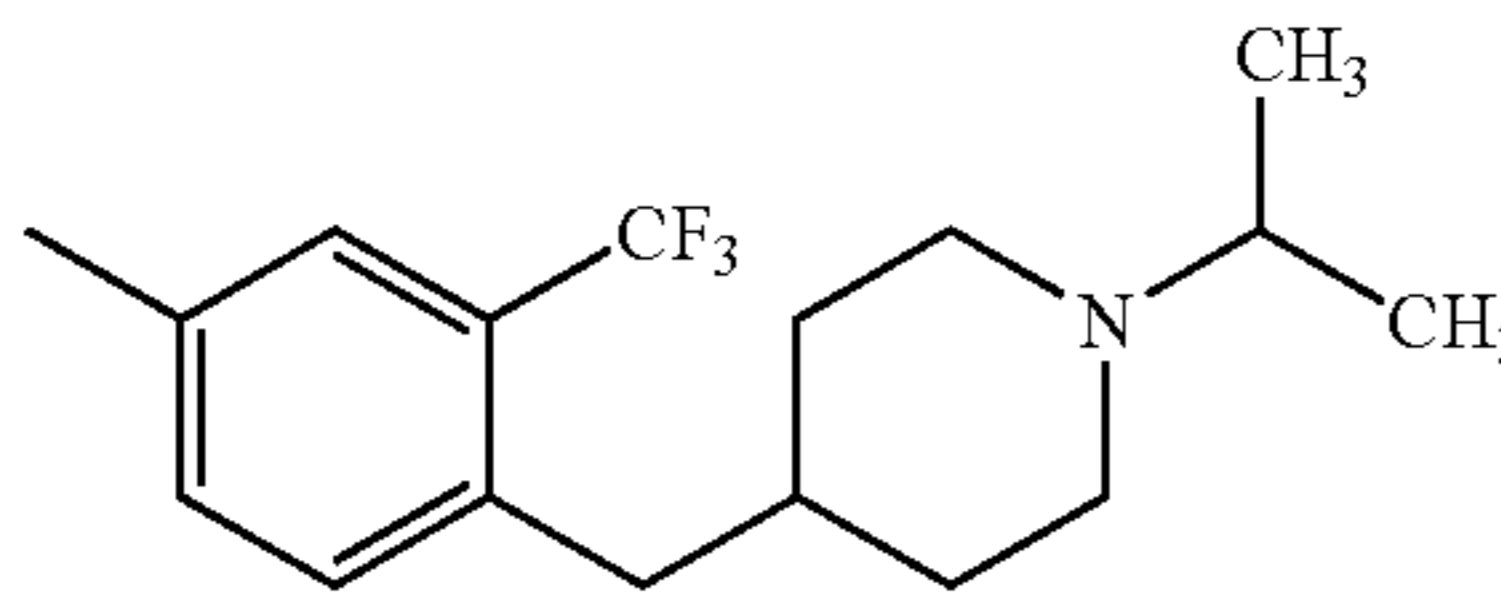
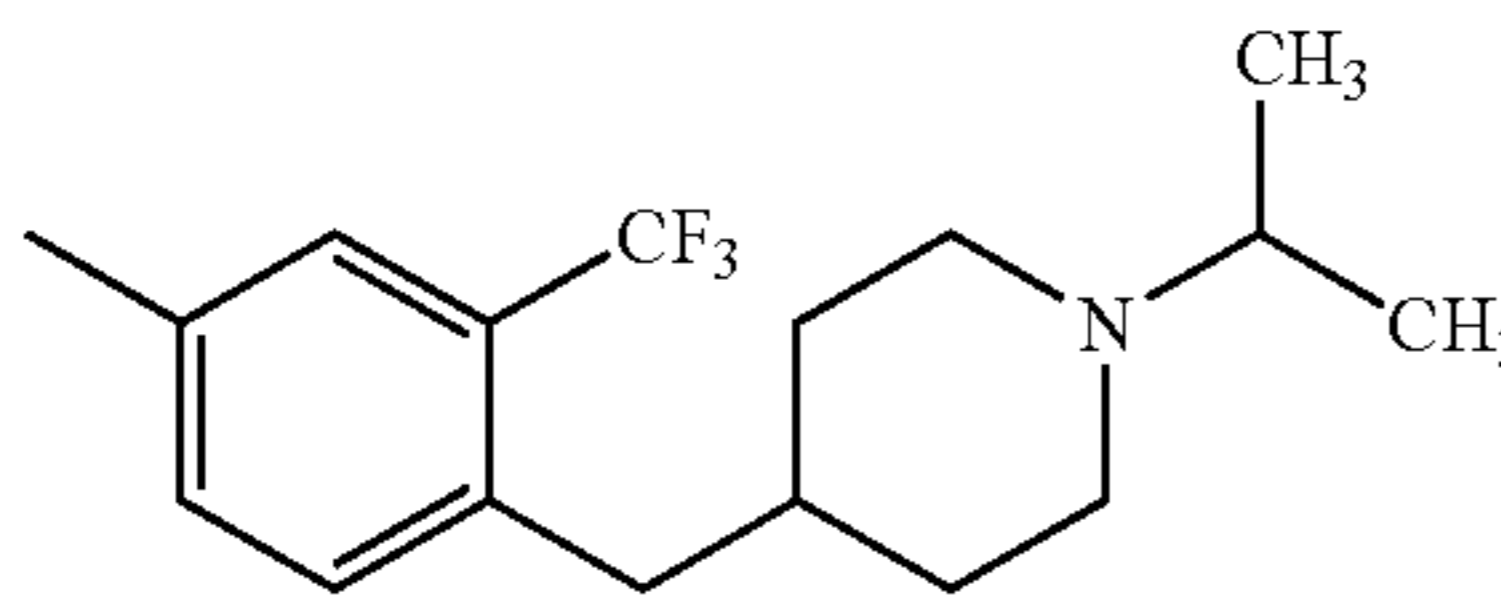
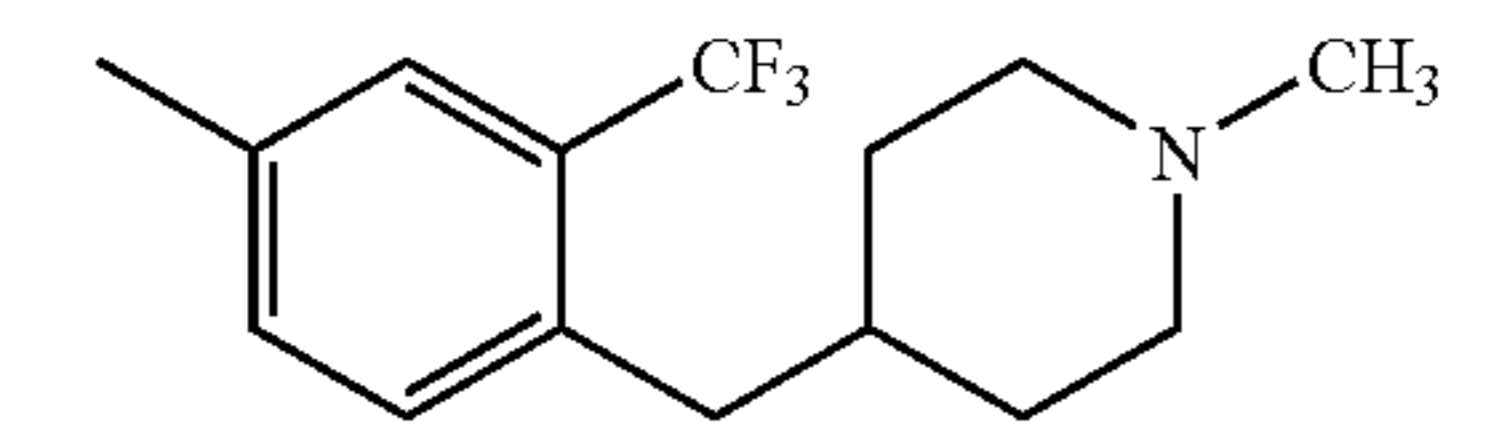
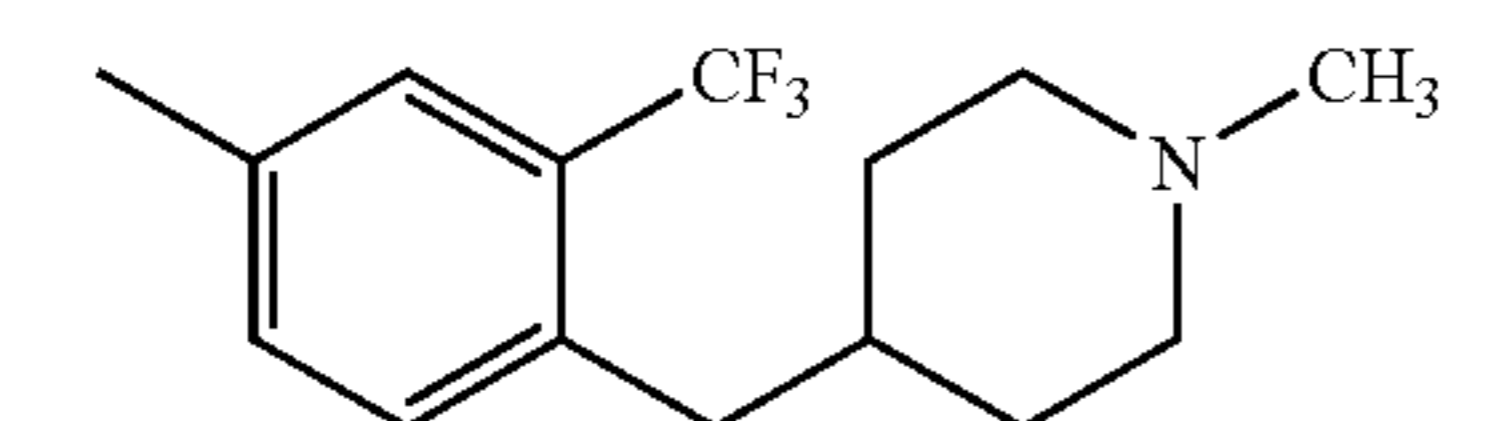
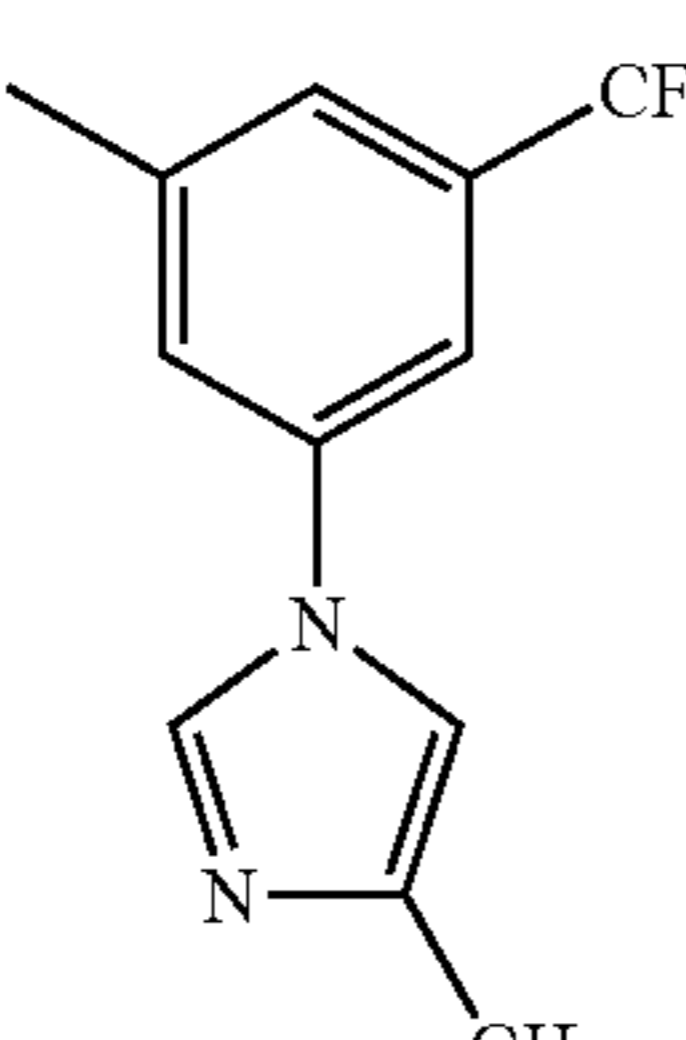
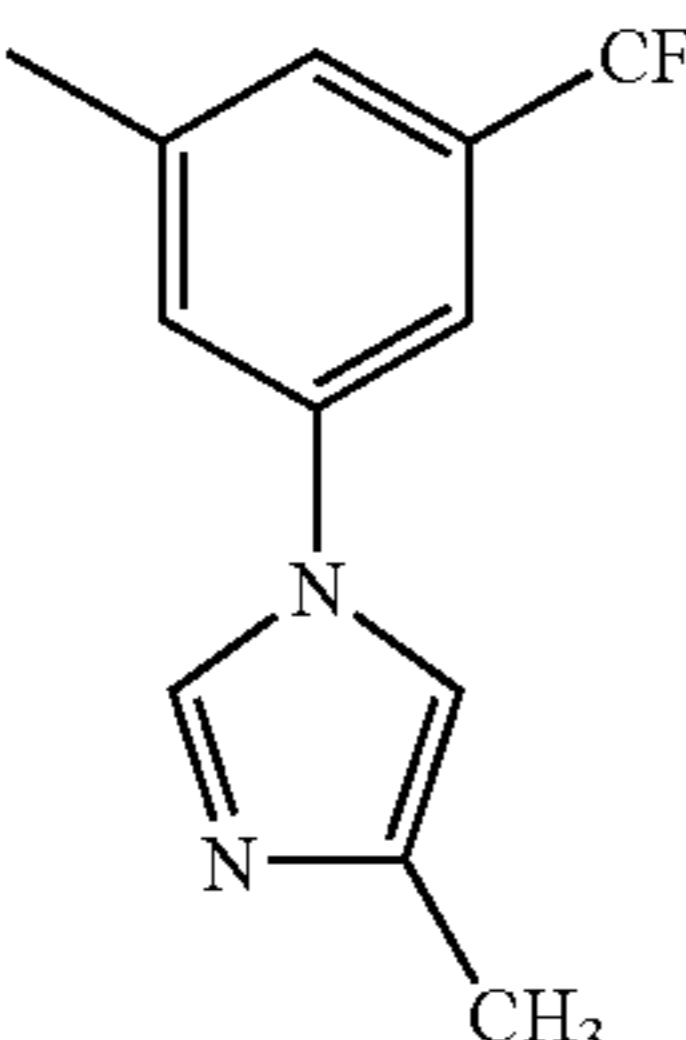
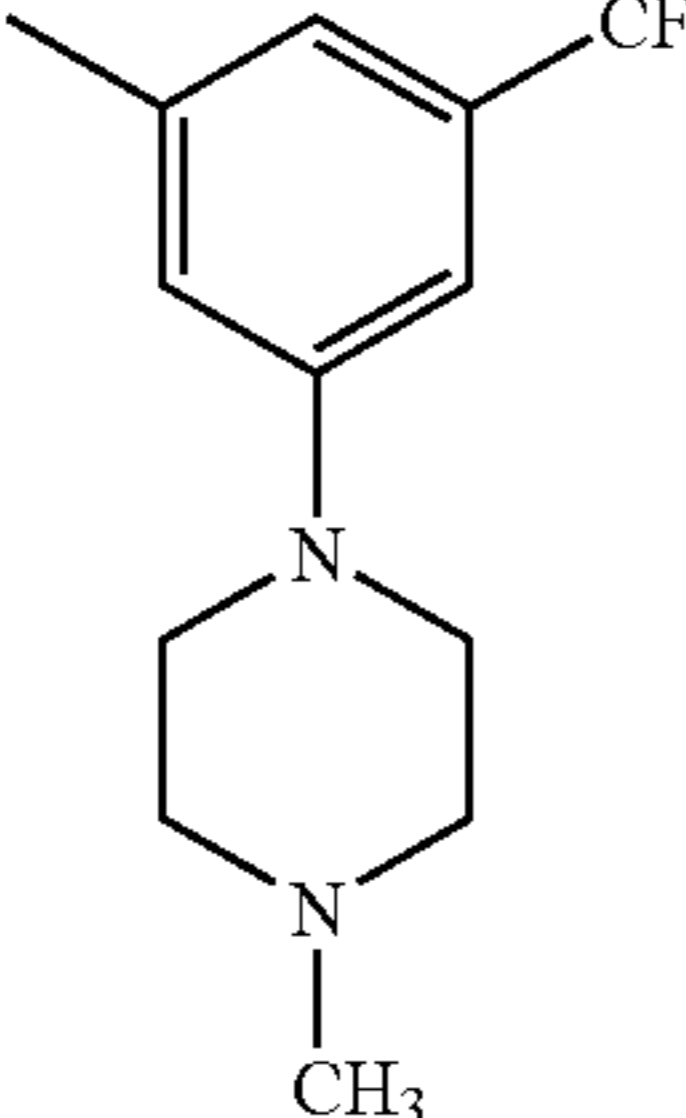
EX X	R ₂	Q	Analytical data
5	N	H	ES-MS: 441.1 [M + H] ⁺ t _R = 2.68 min (System 1); R _f = 0.11 (CH ₂ Cl ₂ /MeOH/NH ₃ ^{aq} , 92:7:1)



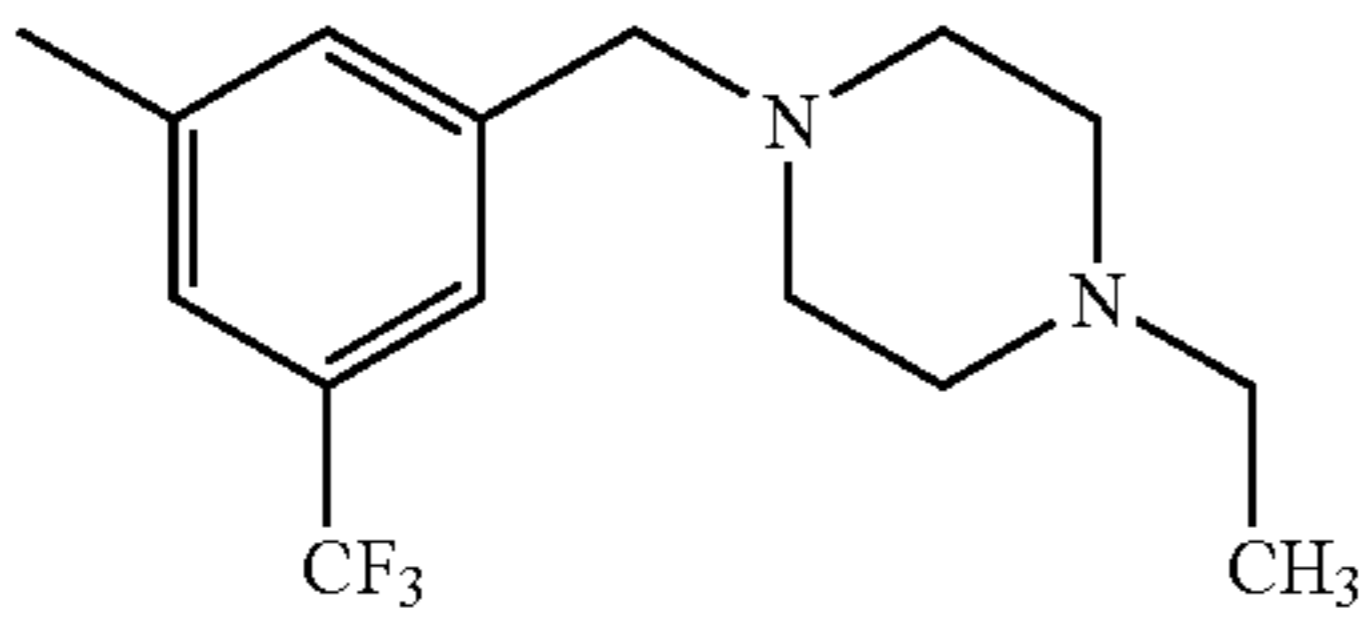
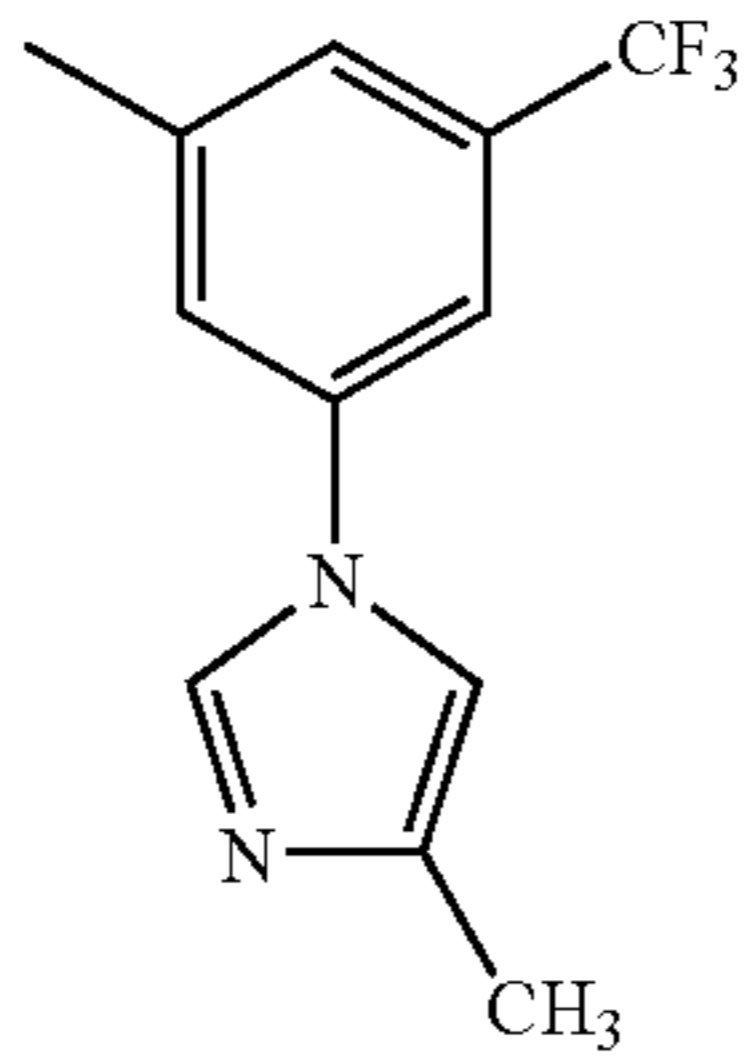
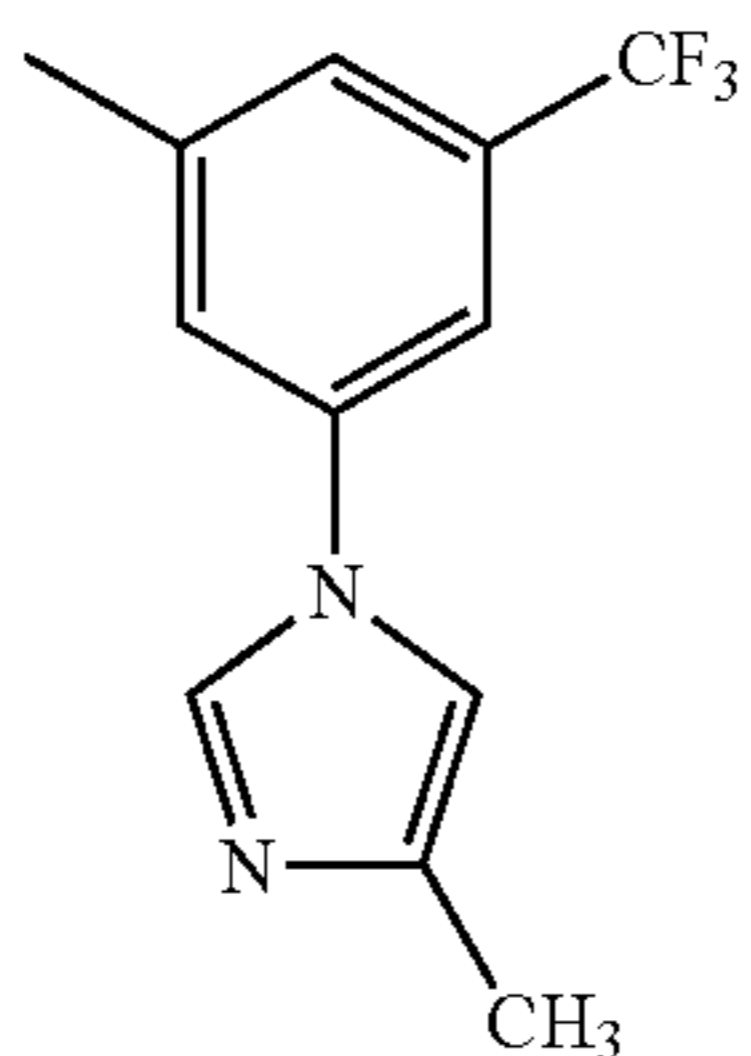
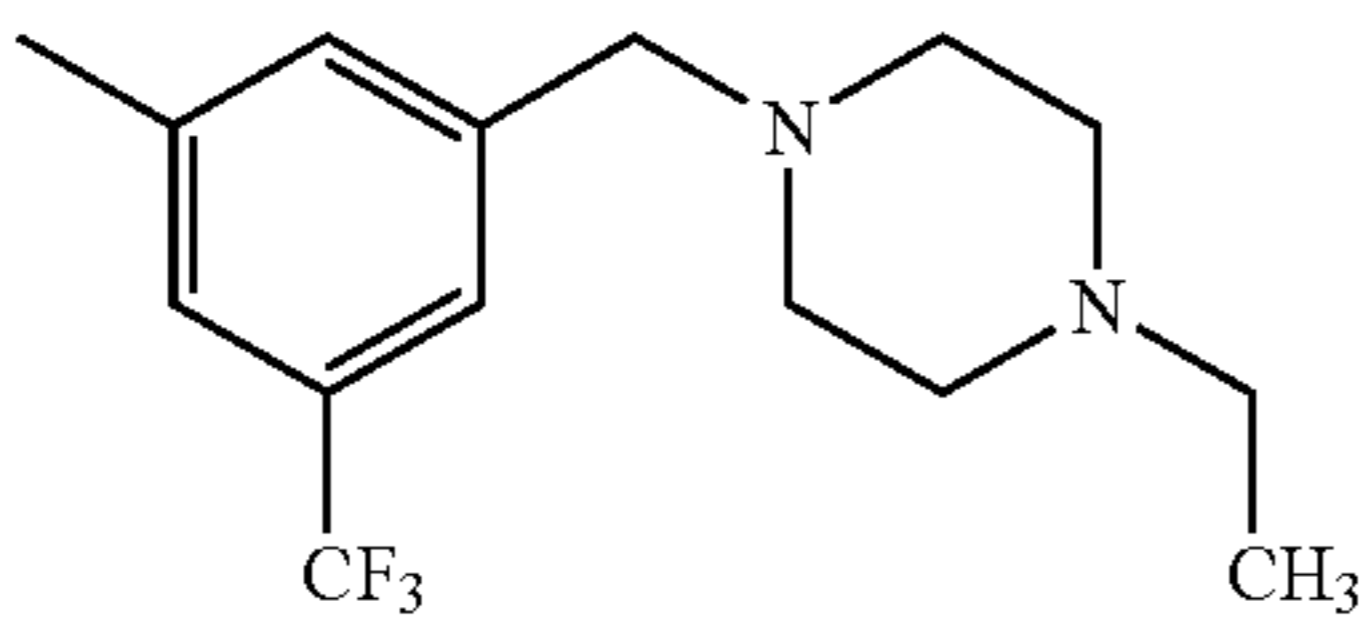
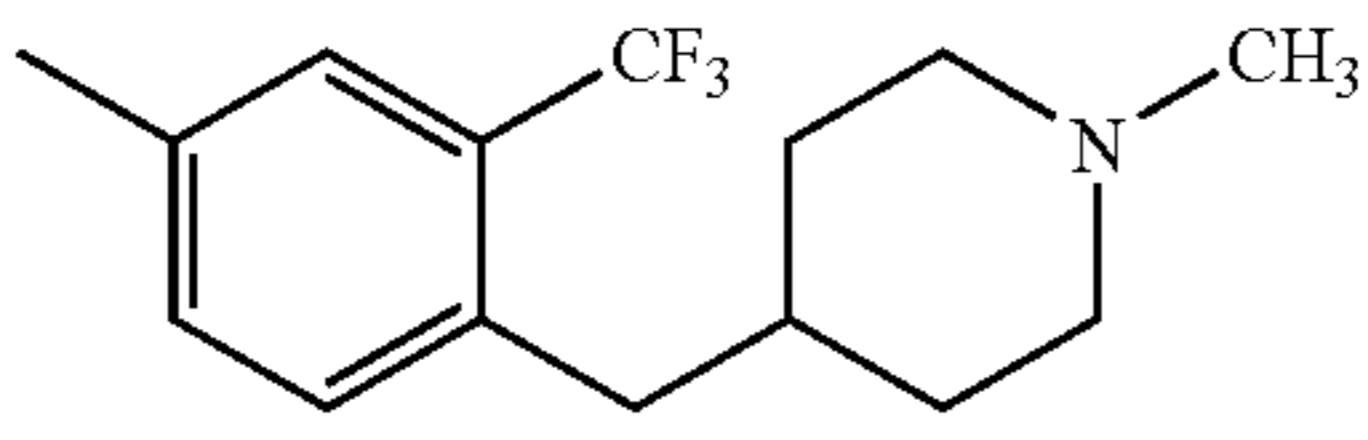
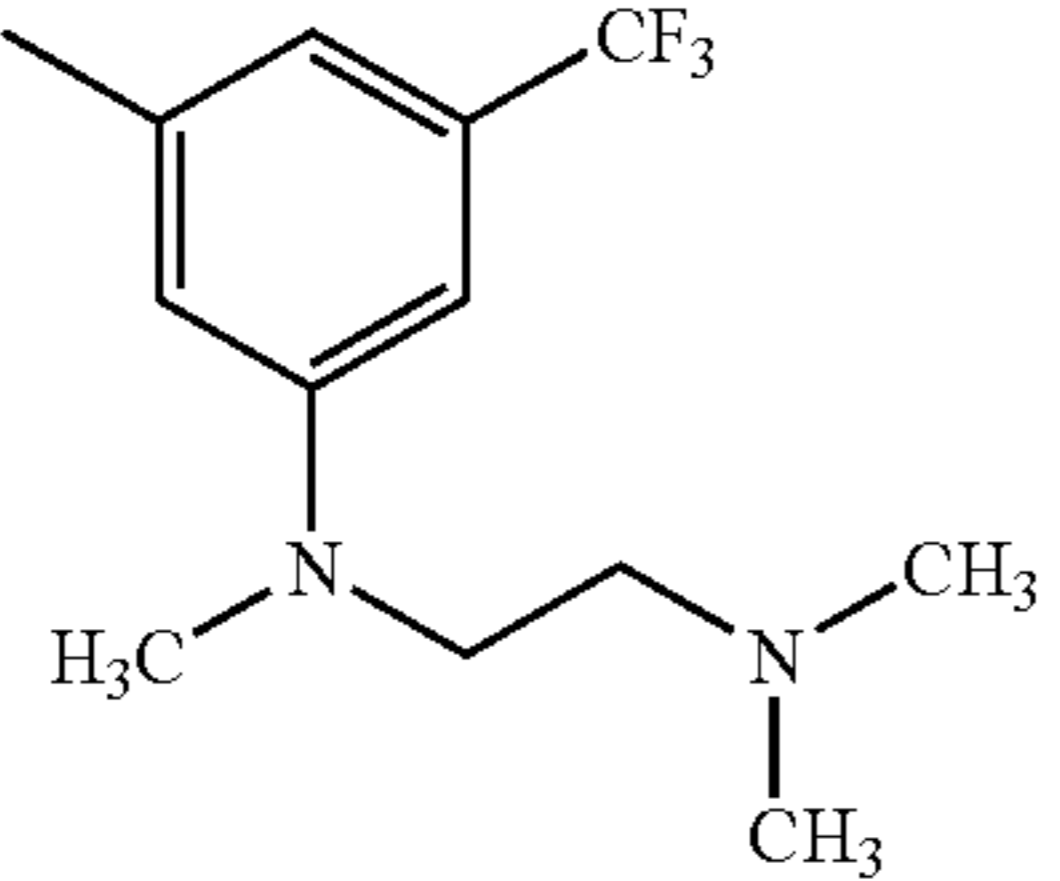
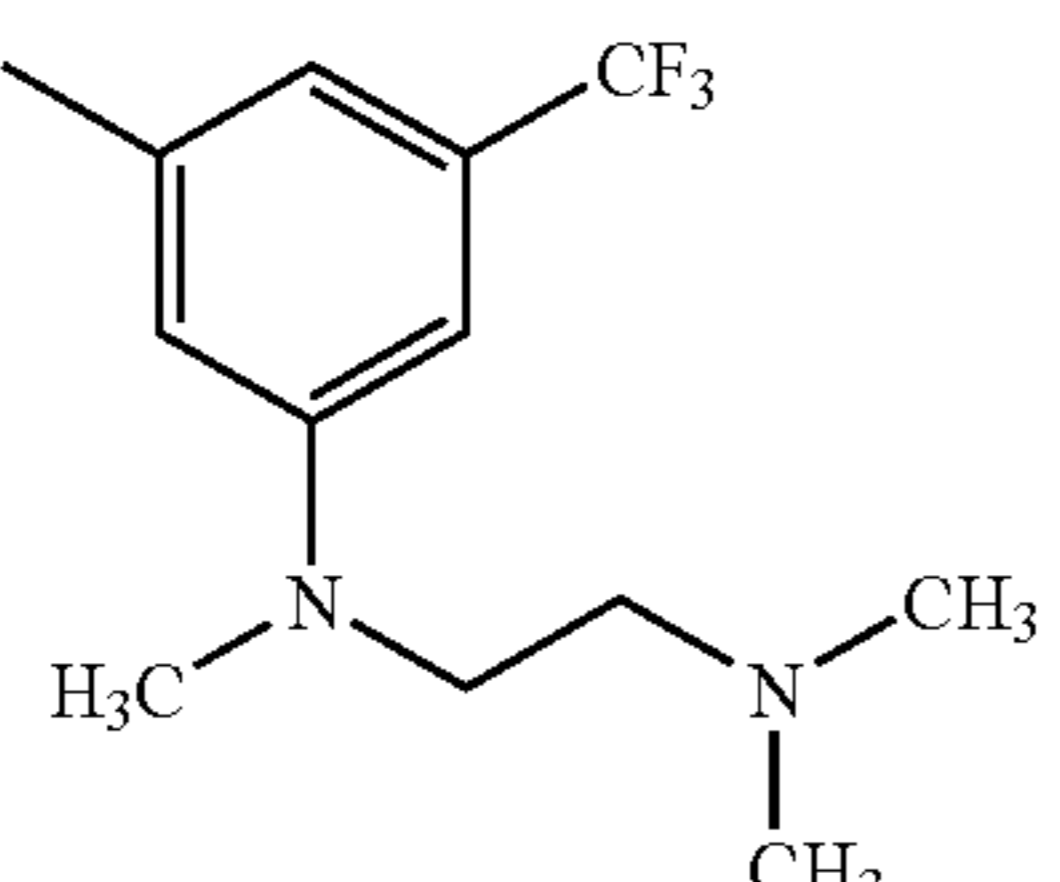
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EX X	R2	Q	Analytical data
6	CH H		ES-MS: 536.0 [M + H] ⁺ ; t _R = 2.68 min (System 1); R _f = 0.29 (CH ₂ Cl ₂ /MeOH, 9:1 + 0.1% NH ₃ ^{aq})
7	N H		ES-MS: 508.0 [M + H] ⁺ ; t _R = 3.32 min (System 1); R _f = 0.09 (CH ₂ Cl ₂ /MeOH/NH ₃ ^{aq} , 91:8:1)
8	CH H		ES-MS: 481.0 [M + H] ⁺ ; t _R = 2.97 min (System 1); R _f = 0.40 (CH ₂ Cl ₂ /MeOH, 9:1)
9	CH H		ES-MS: 479.0 [M + H] ⁺ ; t _R = 2.92 min (System 1); R _f = 0.23 (CH ₂ Cl ₂ /MeOH, 9:1)
10	N Cl		ES-MS: 515.9/517.9 [M + H] ⁺ ; t _R = 3.54 min (System 1); R _f = 0.34 (CH ₂ Cl ₂ /MeOH, 95:5)
11	N Cl		ES-MS: 513.9/515.9 [M + H] ⁺ ; t _R = 3.48 min (System 1); R _f = 0.20 (CH ₂ Cl ₂ /MeOH, 9:1)
12	N H		ES-MS: 522.9 [M + H] ⁺ ; t _R = 3.01 min (System 1); R _f = 0.15 (CH ₂ Cl ₂ /MeOH, 9:1)
13	N H		ES-MS: 482.0 [M + H] ⁺ ; t _R = 3.32 min (System 1); R _f = 0.28 (CH ₂ Cl ₂ /MeOH, 95:5)
14	CH H		ES-MS: 481.0 [M + H] ⁺ ; t _R = 3.12 min (System 1); R _f = 0.14 (CH ₂ Cl ₂ /MeOH, 95:5)
15	N H		ES-MS: 522.0 [M + H] ⁺ ; t _R = 3.41 min (System 1); R _f = 0.22 (CH ₂ Cl ₂ /MeOH/NH ₃ ^{aq} , 94:5:1)
16	CH H		ES-MS: 521.0 [M + H] ⁺ ; t _R = 3.22 min (System 1); R _f = 0.36 (CH ₂ Cl ₂ /MeOH/NH ₃ ^{aq} , 89:10:1)
17	N Cl		ES-MS: 555.9/557.9 [M + H] ⁺ ; t _R = 3.80 min (System 1); R _f = 0.29 (CH ₂ Cl ₂ /MeOH/NH ₃ ^{aq} , 94:5:1)

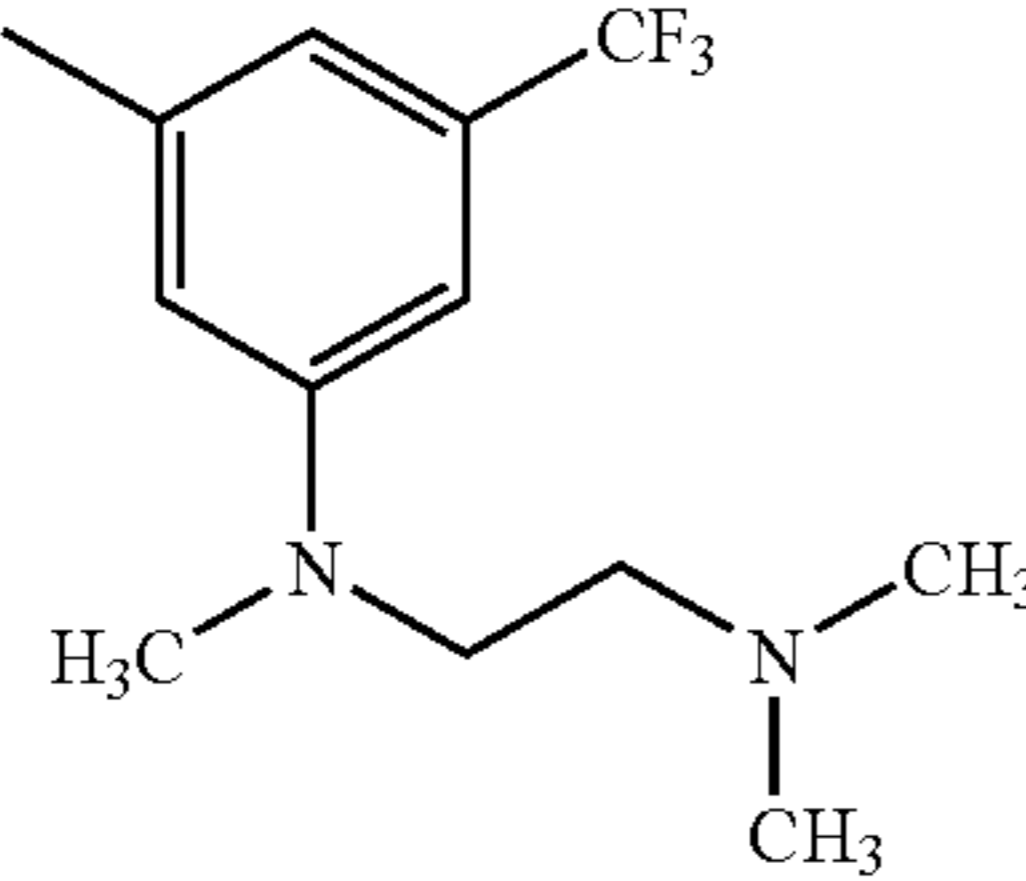
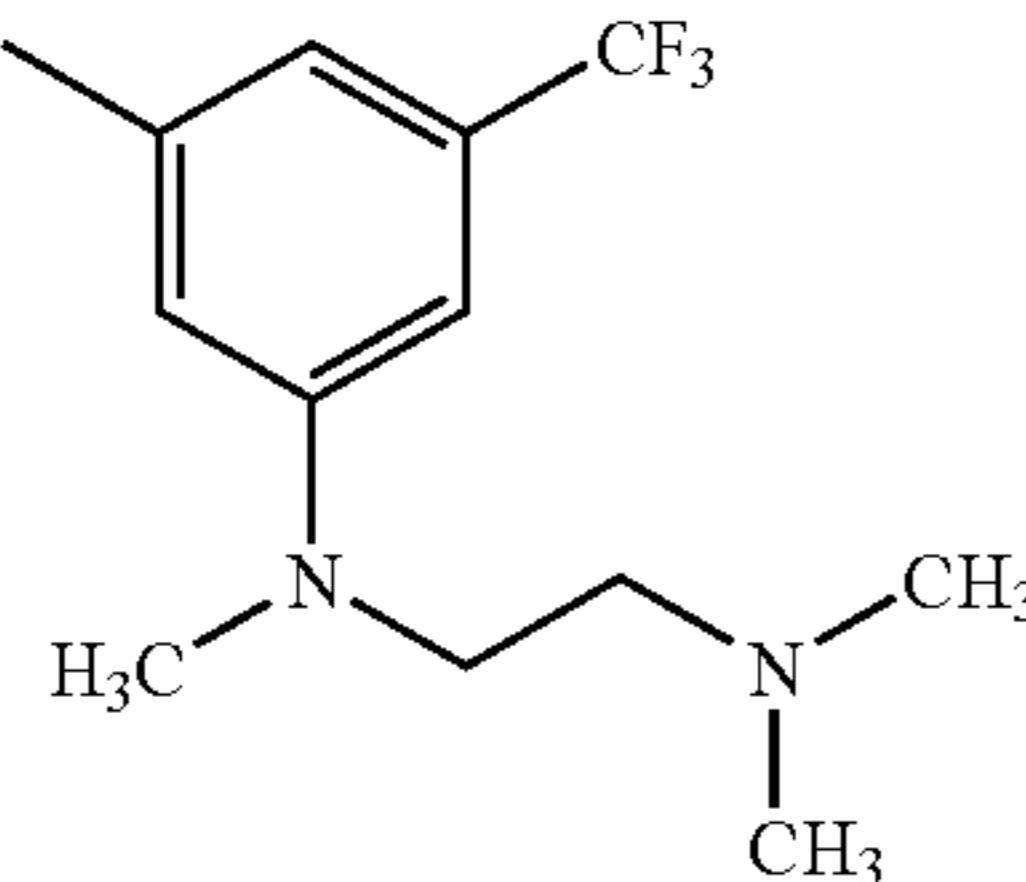
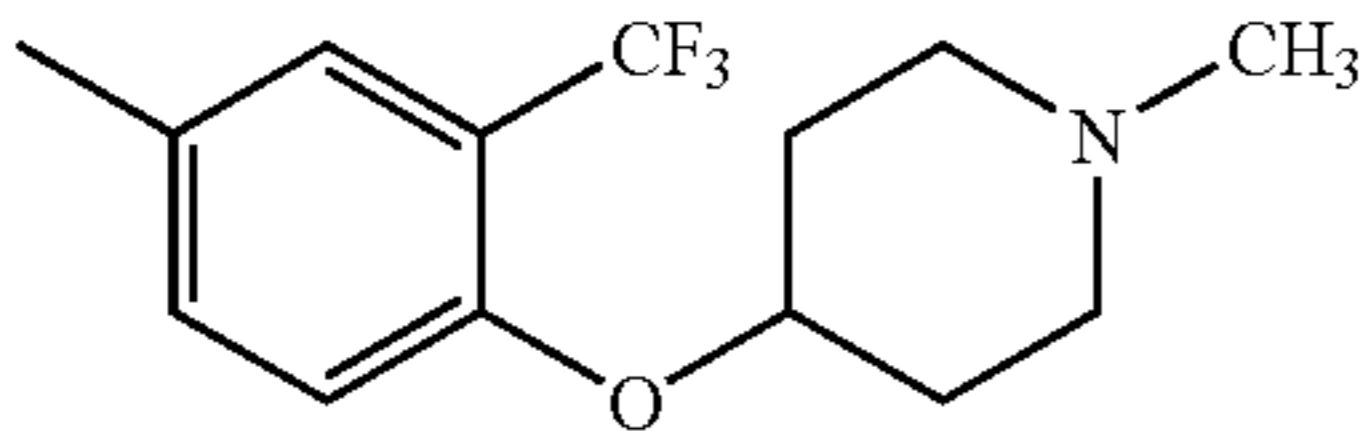
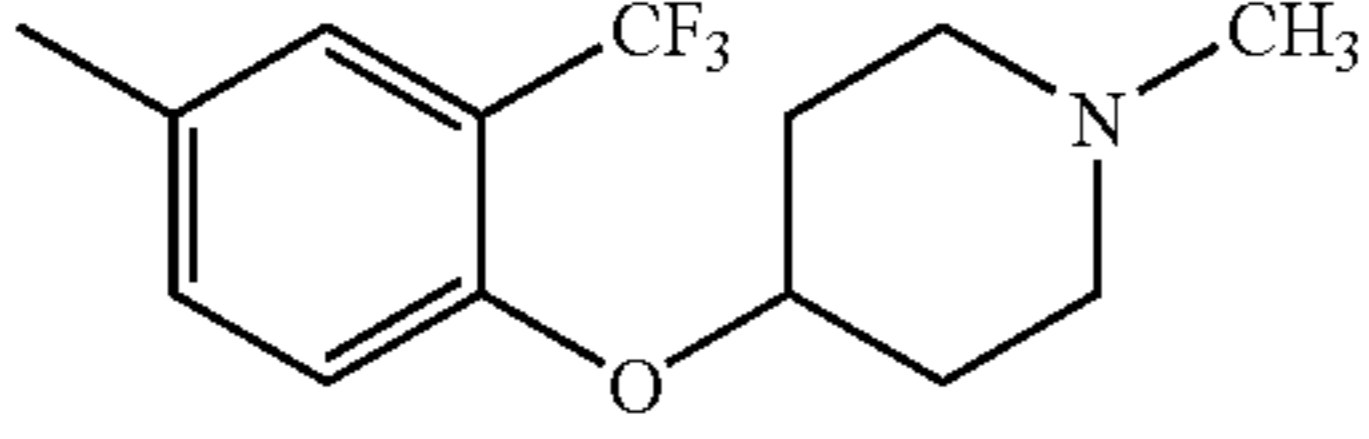
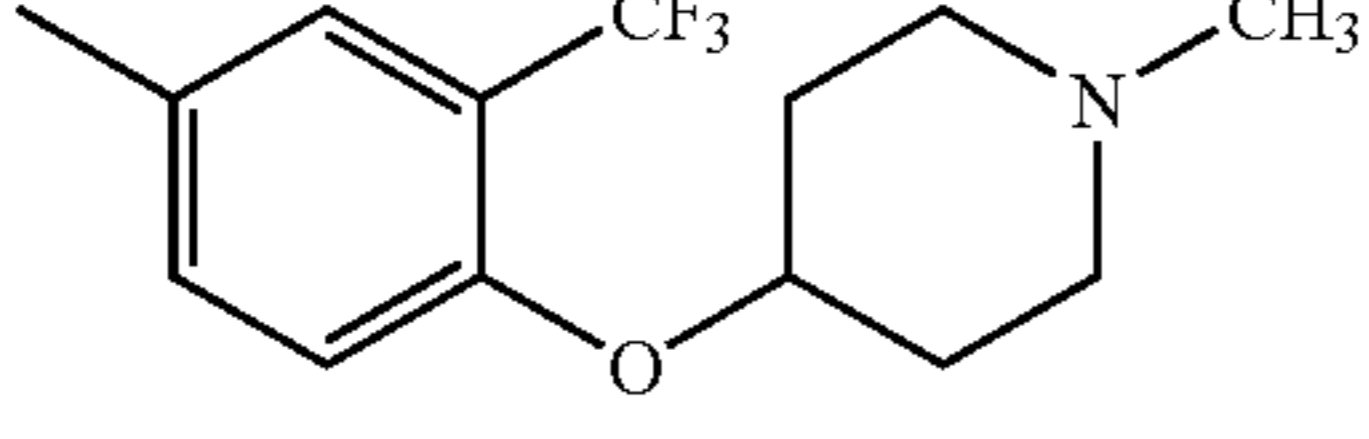
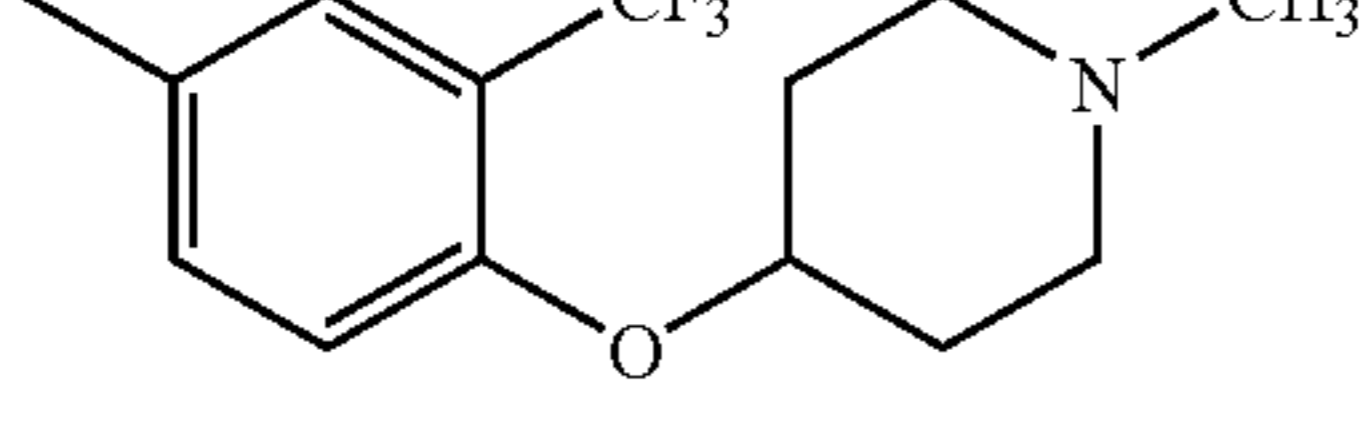
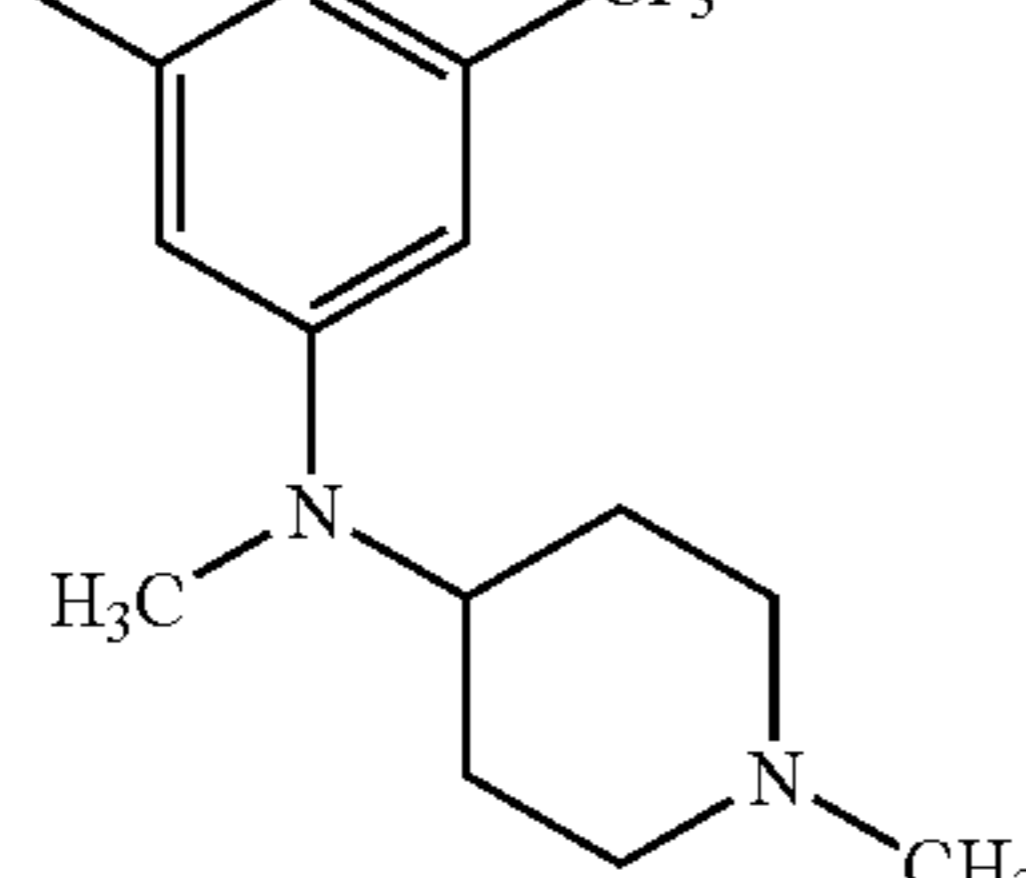
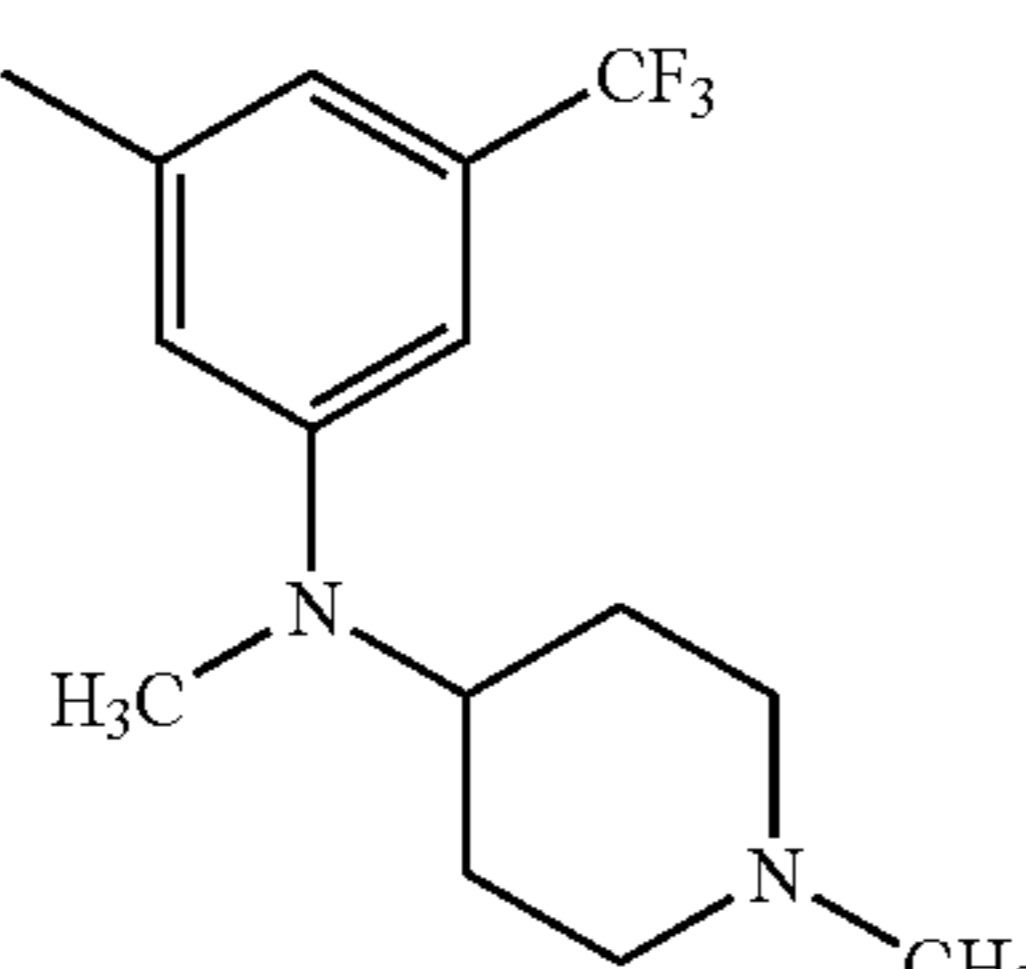
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EX	X	R2	Q	Analytical data
18	N	Cl		ES-MS: 569.9/571.9 [M + H] ⁺ ; t _R = 3.91 min (System 1); R _f = 0.22 (CH ₂ Cl ₂ /MeOH/NH ₃ ^{aq} , 94:5:1)
19	N	H		ES-MS: 536.0 [M + H] ⁺ ; t _R = 3.54 min (System 1); R _f = 0.23 (CH ₂ Cl ₂ /MeOH/NH ₃ ^{aq} , 94:5:1)
20	CH	H		ES-MS: 535.0 [M + H] ⁺ ; t _R = 3.33 min (System 1); R _f = 0.22 (CH ₂ Cl ₂ /MeOH/NH ₃ ^{aq} , 94:5:1)
21	N	Cl		ES-MS: 541.9/543.9 [M + H] ⁺ ; t _R = 3.67 min (System 1); R _f = 0.33 (CH ₂ Cl ₂ /MeOH/NH ₃ ^{aq} , 94:5:1)
22	CH	H		ES-MS: 507.0 [M + H] ⁺ ; t _R = 3.08 min (System 1); R _f = 0.18 (CH ₂ Cl ₂ /MeOH/NH ₃ ^{aq} , 94:5:1)
23	N	H		ES-MS: 476.9 [M + H] ⁺ ; t _R = 3.25 min (System 1); R _f = 0.23 (CH ₂ Cl ₂ /MeOH/NH ₃ ^{aq} , 94:5:1)
24	N	CH ₃		ES-MS: 490.9 [M + H] ⁺ ; t _R = 3.37 min (System 1); R _f = 0.18 (CH ₂ Cl ₂ /MeOH/NH ₃ ^{aq} , 94:5:1)
25	N	CH ₃		ES-MS: 508.9 [M + H] ⁺ ; t _R = 3.35 min (System 1); R _f = 0.40 (CH ₂ Cl ₂ /MeOH/NH ₃ ^{aq} , 94:5:1)

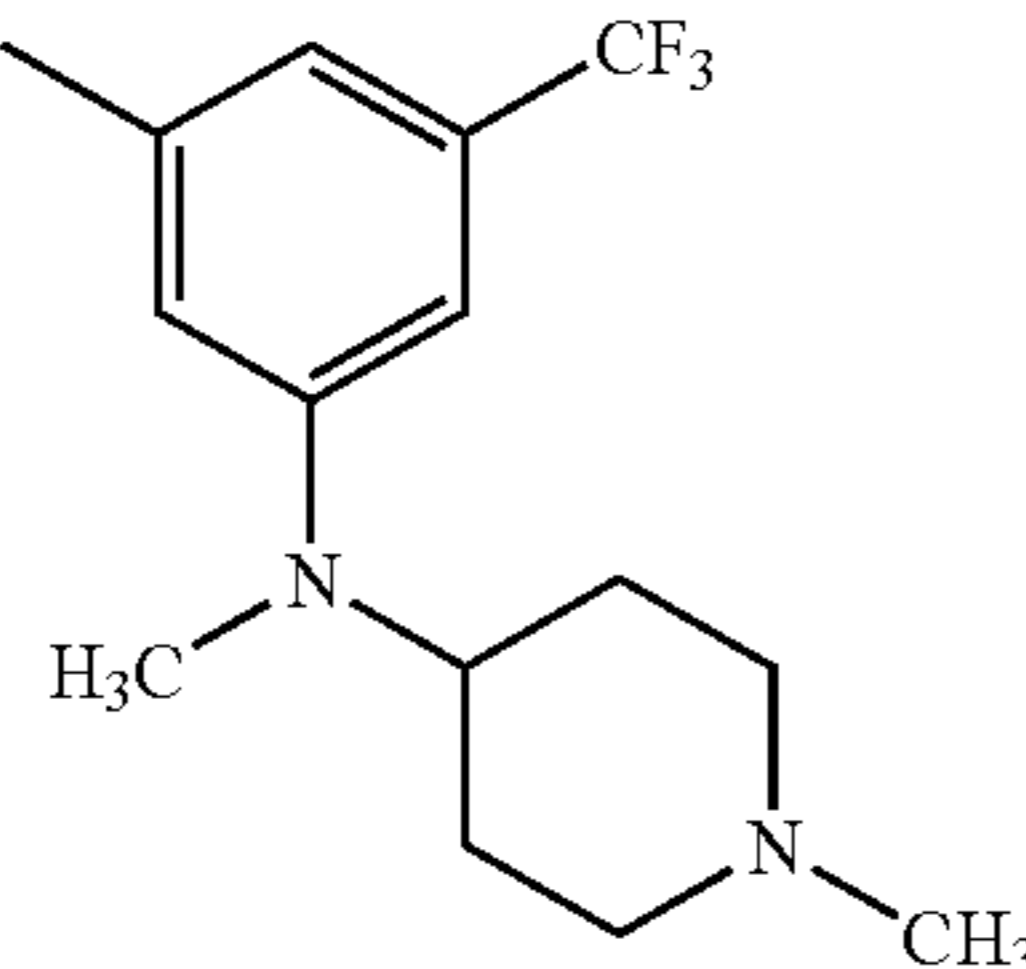
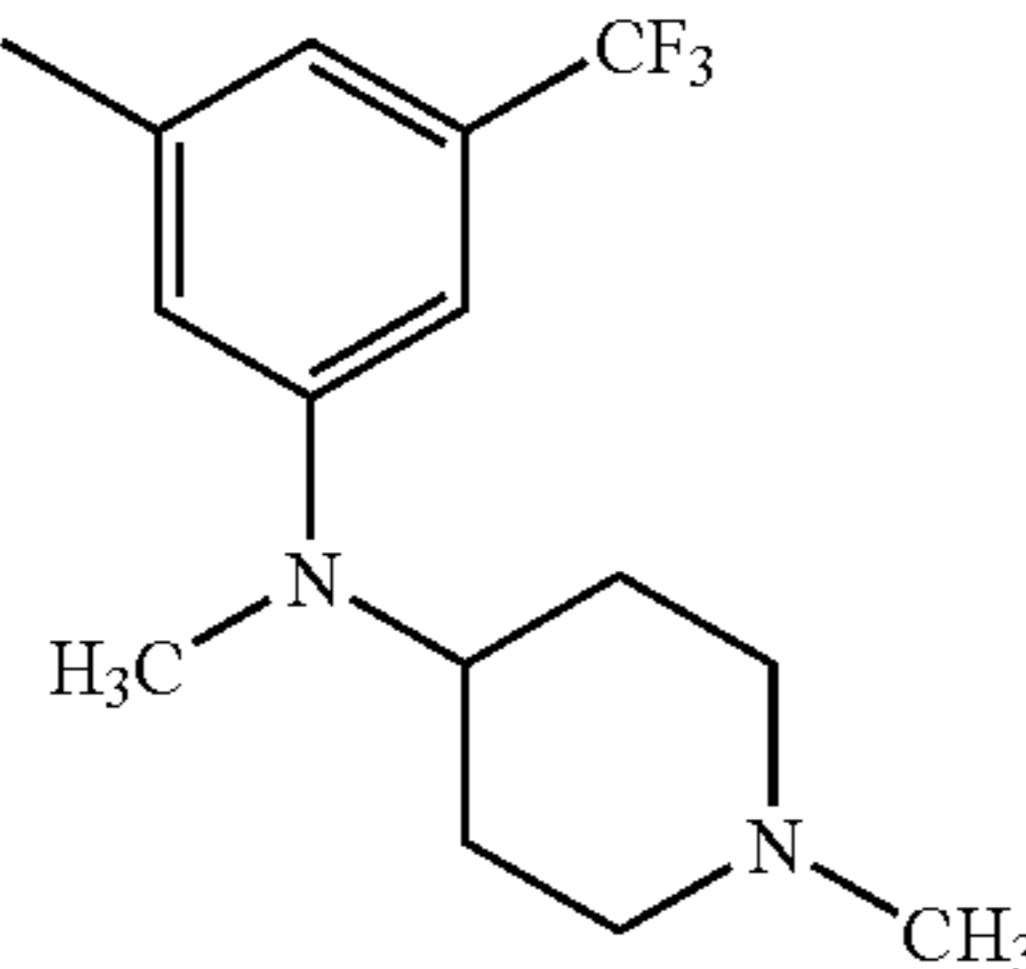
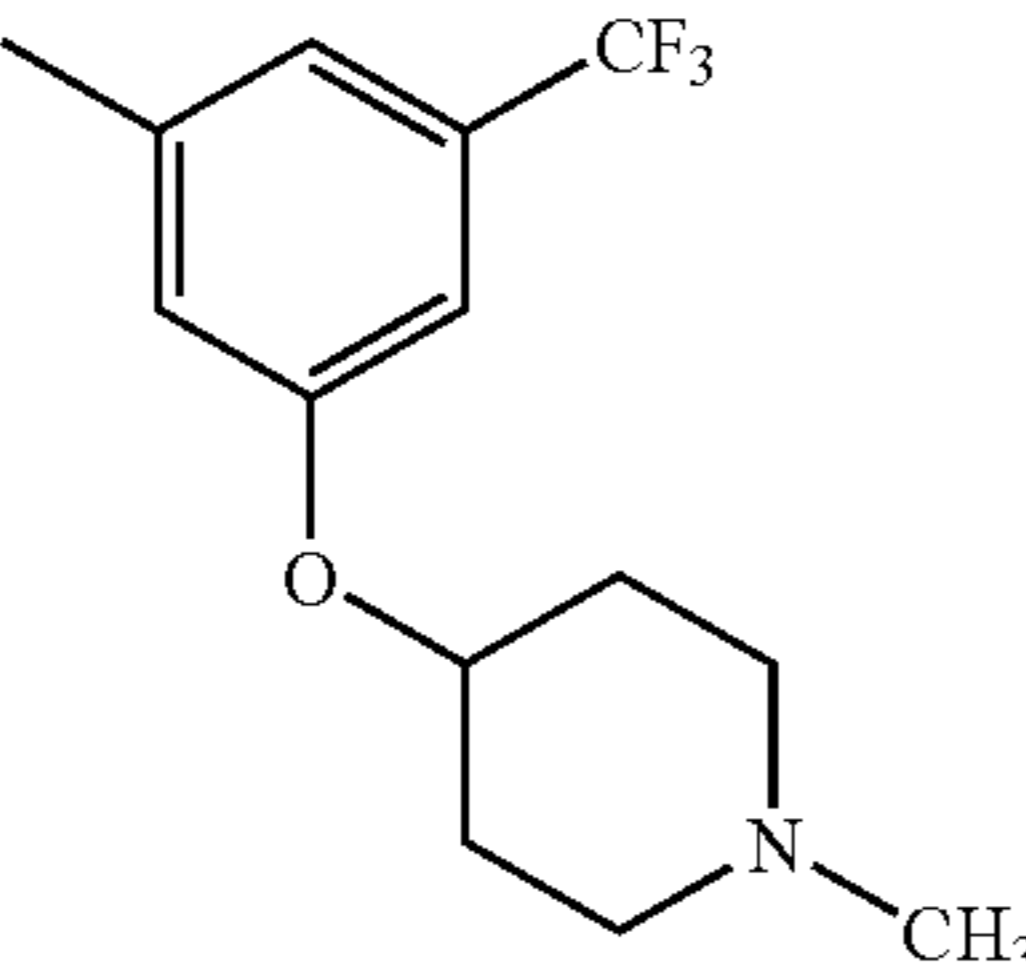
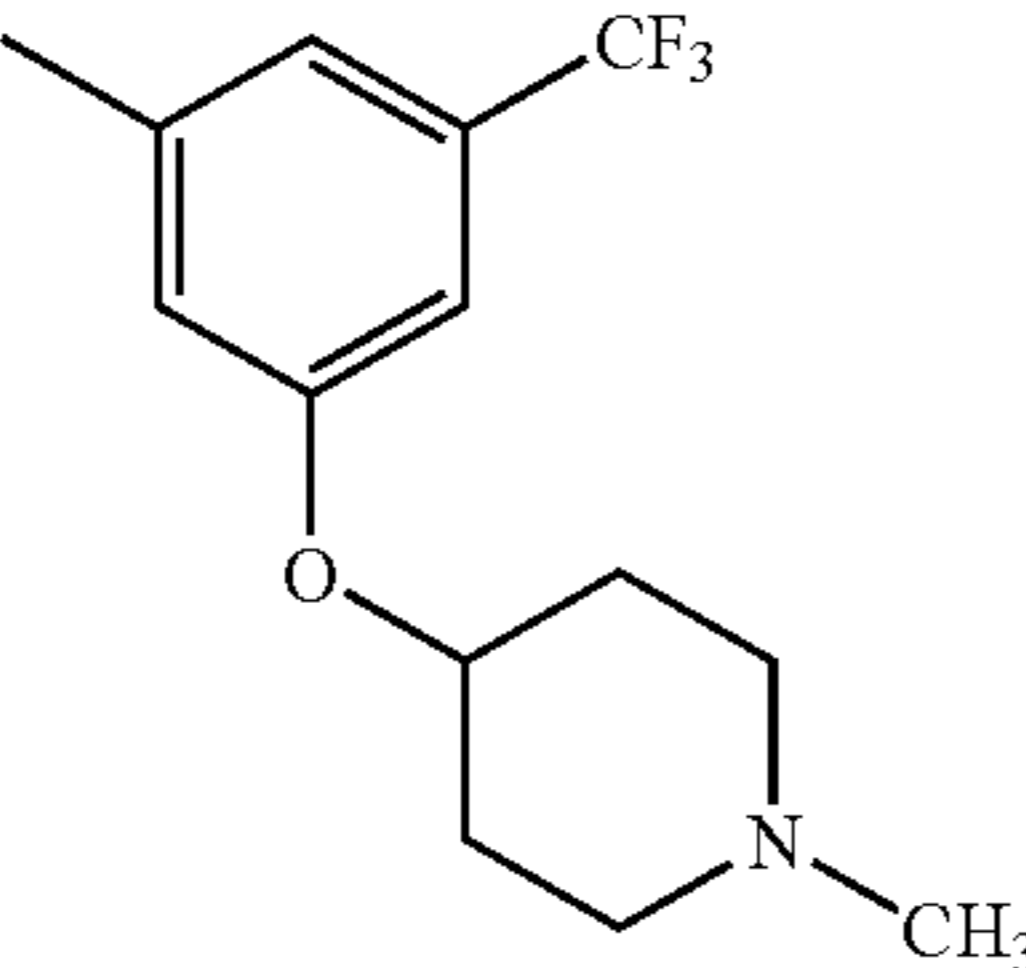
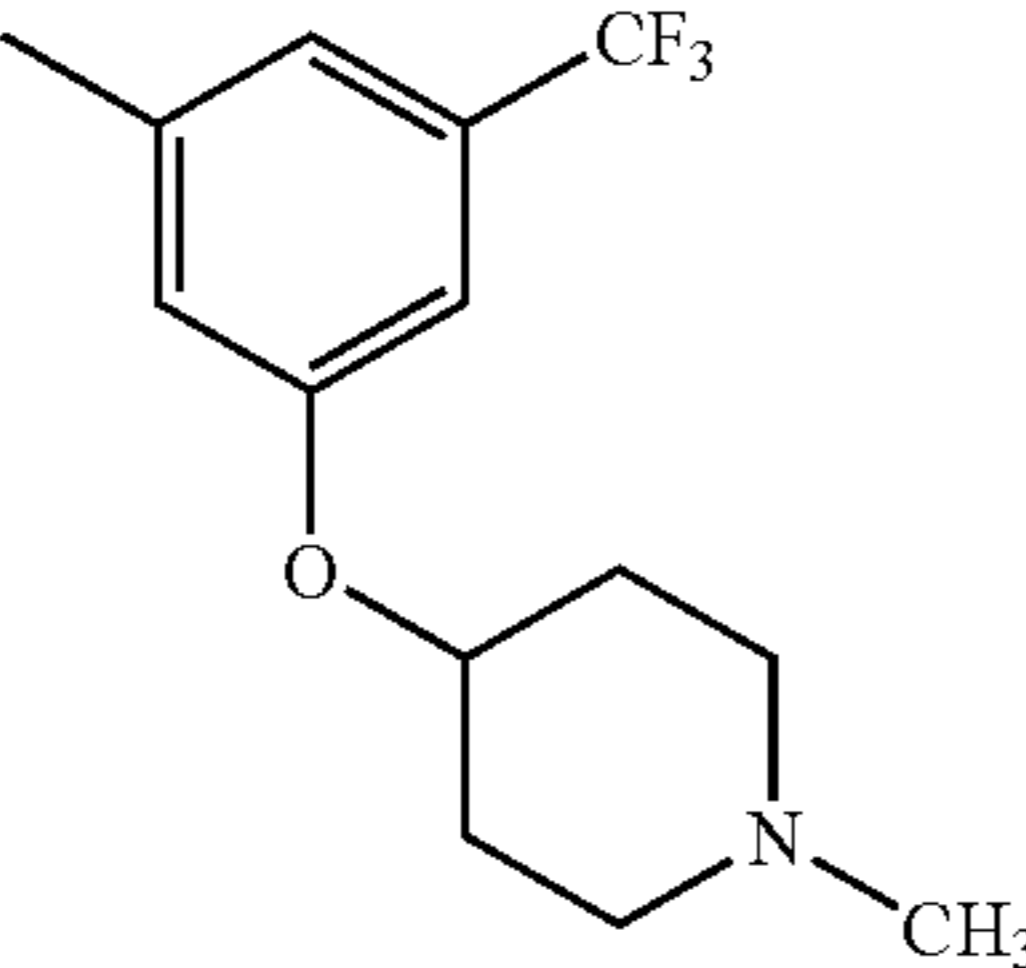
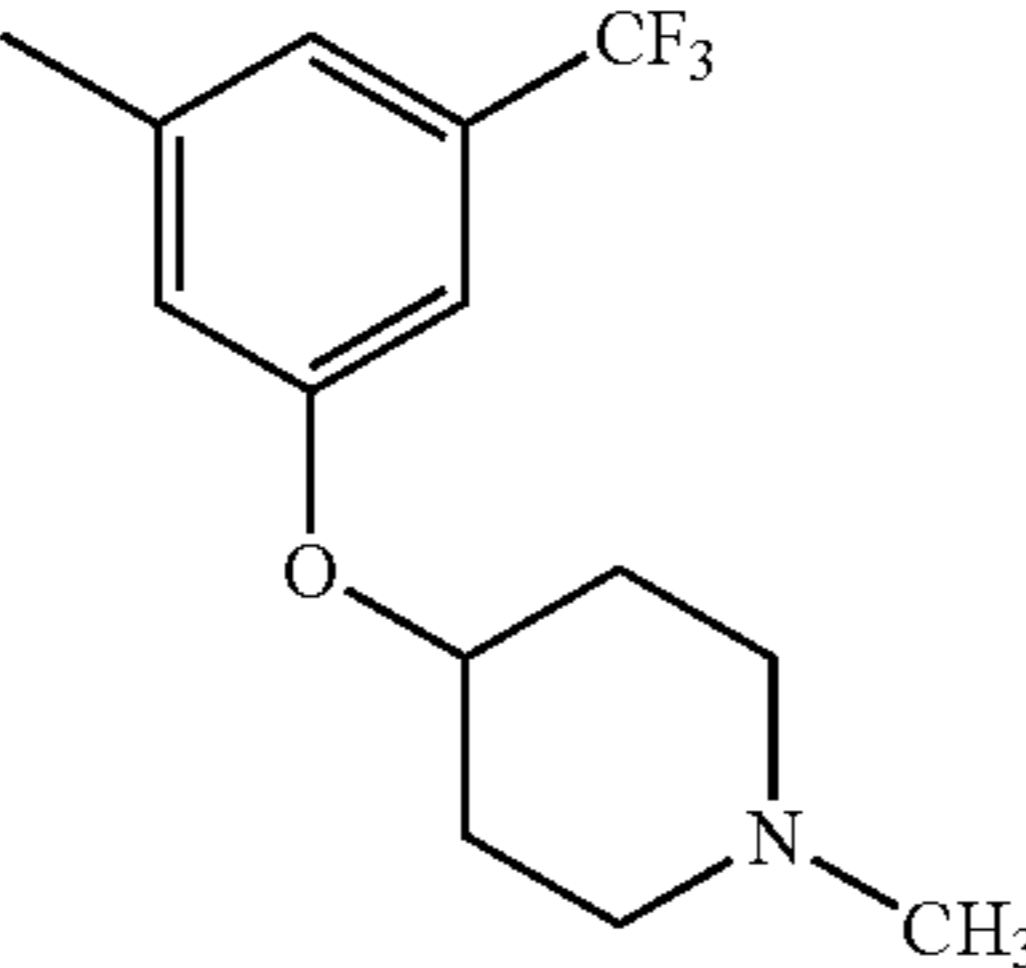
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EX	X	R2	Q	Analytical data
26	N	CH ₃		ES-MS: 536.9 [M + H] ⁺ ; t _R = 3.09 min (System 1); R _f = 0.13 (CH ₂ Cl ₂ /MeOH/NH ₃ ^{aq} , 94:5:1)
27	N	Cl		ES-MS: 510.8/512.8 [M + H] ⁺ ; t _R = 3.60 min (System 1); R _f = 0.26 (CH ₂ Cl ₂ /MeOH/NH ₃ ^{aq} , 94:5:1)
28	CH	H		ES-MS: 475.9 [M + H] ⁺ ; t _R = 3.07 min (System 1)
29	CH	H		ES-MS: 522.0 [M + H] ⁺ ; t _R = 2.89 min (System 1); R _f = 0.20 (CH ₂ Cl ₂ /MeOH/NH ₃ ^{aq} , 94:5:1)
30	N	CH ₃		ES-MS: 522.0 [M + H] ⁺ ; t _R = 3.45 min (System 1); R _f = 0.08 (CH ₂ Cl ₂ /MeOH/NH ₃ ^{aq} , 94:5:1)
31	N	Cl		ES-MS: 531.0/533.2 [M + H] ⁺ ; t _R = 3.75 min (System 1); R _f = 0.31 (CH ₂ Cl ₂ /MeOH/NH ₃ ^{aq} , 94:5:1)
32	N	CH ₃		ES-MS: 511.1 [M + H] ⁺ ; t _R = 3.53 min (System 1)

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EX	X	R2	Q	Analytical data
33	N	H		ES-MS: 497.1 [M + H] ⁺ ; t _R = 3.41 min (System 1)
34	CH	H		ES-MS: 496.1 [M + H] ⁺ ; t _R = 3.23 min (System 1); R _f = 0.18 (CH ₂ Cl ₂ /MeOH/NH ₃ ^{aq} , 94:5:1)
35	CH	H		ES-MS: 509.1 [M + H] ⁺ ; t _R = 3.01 min (System 1); R _f = 0.13 (CH ₂ Cl ₂ /MeOH, 1:1)
36	N	H		ES-MS: 509.9 [M + H] ⁺ ; t _R = 3.19 min (System 1); R _f = 0.05 (CH ₂ Cl ₂ /MeOH, 1:1)
37	N	CH ₃		ES-MS: 524.1 [M + H] ⁺ ; t _R = 3.30 min (System 1)
38	N	Cl		ES-MS: 544.0 [M + H] ⁺ ; t _R = 3.57 min (System 1)
39	N	Cl		ES-MS: 557.1 [M + H] ⁺ ; t _R = 3.80 min (System 1)
40	N	CH ₃		ES-MS: 537.1 [M + H] ⁺ ; t _R = 3.57 min (System 1)

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EX	X	R2	Q	Analytical data
41	N	H		ES-MS: 523.1 [M + H] ⁺ ; t _R = 3.45 min (System 1)
42	CH	H		ES-MS: 522.1 [M + H] ⁺ ; t _R = 3.29 min (System 1)
43	N	Cl		ES-MS: 544.0 [M + H] ⁺ ; t _R = 3.76 min (System 1)
44	N	CH ₃		ES-MS: 524.2 [M + H] ⁺ ; t _R = 3.53 min (System 1)
45	N	H		ES-MS: 510.1 [M + H] ⁺ ; t _R = 3.42 min (System 1)
46	CH	H		ES-MS: 509.1 [M + H] ⁺ ; t _R = 3.22 min (System 1)

57

Starting Materials

3-(4-Ethyl-piperazin-1-yl)-phenylamine

Used for preparing the compound of example 5 may be obtained analogously to a method as described in WO 2006000420. API-ES-MS: 206.2.

4-(4-Isopropyl-piperazin-1-ylmethyl)-3-trifluoromethyl-phenylamine

Used for preparing the compound of example 6 may be obtained analogously to a method as described in WO2005051366.

4-(1-Methyl-piperidin-4-ylmethyl)-3-trifluoromethyl-phenylamine

Used for preparing the compound of example 7.

A mixture of 6.95 g of 4-(1-methyl-piperidin-4-ylidenemethyl)-3-trifluoromethyl-phenylamine and 2.1 g of platinum on carbon in 150 ml of EtOH is stirred for 45 hours at rt, under a hydrogen atmosphere. The mixture obtained is filtered through celite and concentrated. The concentrate obtained is subjected to silica gel column chromatography (CH₂Cl₂/MeOH/NH₃^{aq}, 91:8:1). 4-(1-Methyl-piperidin-4-ylmethyl)-3-trifluoromethyl-phenylamine is obtained in the form of a solid: ES-MS: 273.1 [M+H]⁺; t_R=1.40 min (System 1); R_f=0.33 (CH₂Cl₂/MeOH/NH₃^{aq}, 91:8:1).

4-(1-Methyl-piperidin-4-ylidenemethyl)-3-trifluoromethyl-phenylamine

Used for preparing the compound of example 7.

2.4 g of NaH, 60% dispersion in mineral oil, are added to a cold (5° C.) solution of 11.15 g of [4-(2,2,2-trifluoro-acetylamino)-2-trifluoromethyl-benzyl]-phosphonic acid diethyl ester in 250 ml of THF under an argon atmosphere and the mixture obtained is stirred at 5° C. To the mixture obtained 3.7 ml of 1-methyl-4-piperidone are added. The mixture obtained is allowed to warm to rt and is stirred for 20 hours. To the mixture obtained 1.0 ml of 1-methyl-4-piperidone are added and the mixture obtained is stirred for 4 hours. To the mixture obtained 800 mg of NaH, 60% dispersion in mineral oil, are added, the mixture obtained is stirred for 2 hours and further 800 mg of NaH, 60% dispersion in mineral oil, are added. The mixture obtained is stirred at rt overnight and quenched by addition of 50 ml of H₂O. The mixture obtained is stirred for 24 hours at rt, concentrated, diluted with EtOAc and H₂O, and extracted with EtOAc. The organic phase obtained is washed with brine, dried (Na₂SO₄), filtered, and concentrated. The concentrate obtained is subjected to silica gel column chromatography (CH₂Cl₂/MeOH/NH₃^{aq}, 89:10:1). 4-(1-Methyl-piperidin-4-ylidenemethyl)-3-trifluoromethyl-phenylamine in the form of an oil is obtained. ES-MS: 271.1 [M+H]⁺; t_R=1.82 min (System 1); R_f=0.32 (CH₂Cl₂/MeOH/NH₃^{aq}, 89:10:1).

[4-(2,2,2-Trifluoro-acetylamino)-2-trifluoromethyl-benzyl]-phosphonic acid diethyl ester

Used for preparing the compound of example 7.

6 ml of triethyl phosphite are added to a suspension of 10 g N-(4-bromomethyl-3-trifluoromethyl-phenyl)-2,2,2-trifluoro-acetamide (obtainable according to WO 2005051366) in 60 ml of toluene. The mixture obtained is stirred for 18 hours at reflux, allowed to cool to rt and concentrated. The

58

concentrate obtained is triturated in Et₂O. [4-(2,2,2-Trifluoro-acetylamino)-2-trifluoromethyl-benzyl]-phosphonic acid diethyl ester is obtained in the form of a solid: ES-MS: 406.0 [M-H]⁻; t_R=4.41 min (System 1).

4-Diethylaminomethyl-3-trifluoromethyl-phenylamine

Used for preparing the compound of examples 8 and 10 may be obtained analogously to a method as described in WO2005051366.

4-Pyrrolidin-1-ylmethyl-3-trifluoromethyl-phenylamine

Used for preparing the compound of examples 9 and 11 may be obtained analogously to a method as described in WO2006034833.

3-(4-Ethyl-piperazin-1-ylmethyl)-5-trifluoromethyl-phenylamine

for preparing the compounds of examples 12, 26 and 29 may be obtained analogously to a method as described in WO2003099771.

3-Diethylaminomethyl-5-trifluoromethyl-phenylamine

for preparing the compound of examples 13 and 14 may be obtained analogously to a method as described in WO2005051366

4-(1-Ethyl-piperidin-4-ylmethyl)-3-trifluoromethyl-phenylamine

for preparing the compound of example 15 may be obtained analogously to a method as described for 4-(1-methyl-piperidin-4-ylmethyl)-3-trifluoromethyl-phenylamine but using appropriate starting materials. ES-MS: 287.1 [M+H]⁺; t_R=1.59 min (System 1); R_f=0.37 (CH₂Cl₂/MeOH/NH₃^{aq}, 89:10:1).

4-(1-Isopropyl-piperidin-4-ylmethyl)-3-trifluoromethyl-phenylamine

for preparing the compound of example 18 may be obtained analogously to a method as described for 4-(1-methyl-piperidin-4-ylmethyl)-3-trifluoromethyl-phenylamine but using appropriate starting materials. ES-MS: 301.2 [M+H]⁺; t_R=1.97 min (System 1).

3-(4-Methyl-imidazol-1-yl)-5-trifluoromethyl-phenylamine

for preparing the compound of examples 23, 24, 27 and 28 may be obtained analogously to a method as described in WO2004005281.

3-(4-Methyl-piperazin-1-yl)-5-trifluoromethyl-phenylamine

for preparing the compound of example 25 may be obtained analogously to a method as described in WO 2005051366.

N-(2-Dimethylamino-ethyl)-N-methyl-5-trifluoromethyl-benzene-1,3-diamine

for preparing the compound of example 31 may be obtained analogously to a method as described in

59

WO2004005281 for 3-(4-methyl-imidazol-1-yl)-5-trifluoromethyl-phenylamine but using appropriate starting materials. ES-MS: 262.3 [M+H]⁺; t_R=1.74 min.

4-(1-Methyl-Piperidin-4-yloxy)-3-trifluoromethyl-phenylamine

for preparing the compounds of examples 35 to 38 may be obtained analogously to a method as described in WO2005051366.

N-Methyl-N-(1-methyl-piperidin-4-yl)-5-trifluoromethyl-benzene-1,3-diamine

for preparing the compound of examples 39 to 42 may be obtained analogously to a method as described in WO2004005281 for 3-(4-methyl-imidazol-1-yl)-5-trifluoromethyl-phenylamine but using appropriate starting materials. ES-MS: 288.2 [M+H]⁺; t_R=1.76 min.

3-(1-Methyl-piperidin-4-yloxy)-5-trifluoromethyl-phenylamine

for preparing the compound of examples 43 to 46 may be obtained analogously to a method as described in WO2004005281 for 3-(4-methyl-imidazol-1-yl)-5-trifluoromethyl-phenylamine, but using 1-methyl-piperidin-4-ol. ES-MS: 275.2 [M+H]⁺; t_R=2.41 min

Example A

Capsules

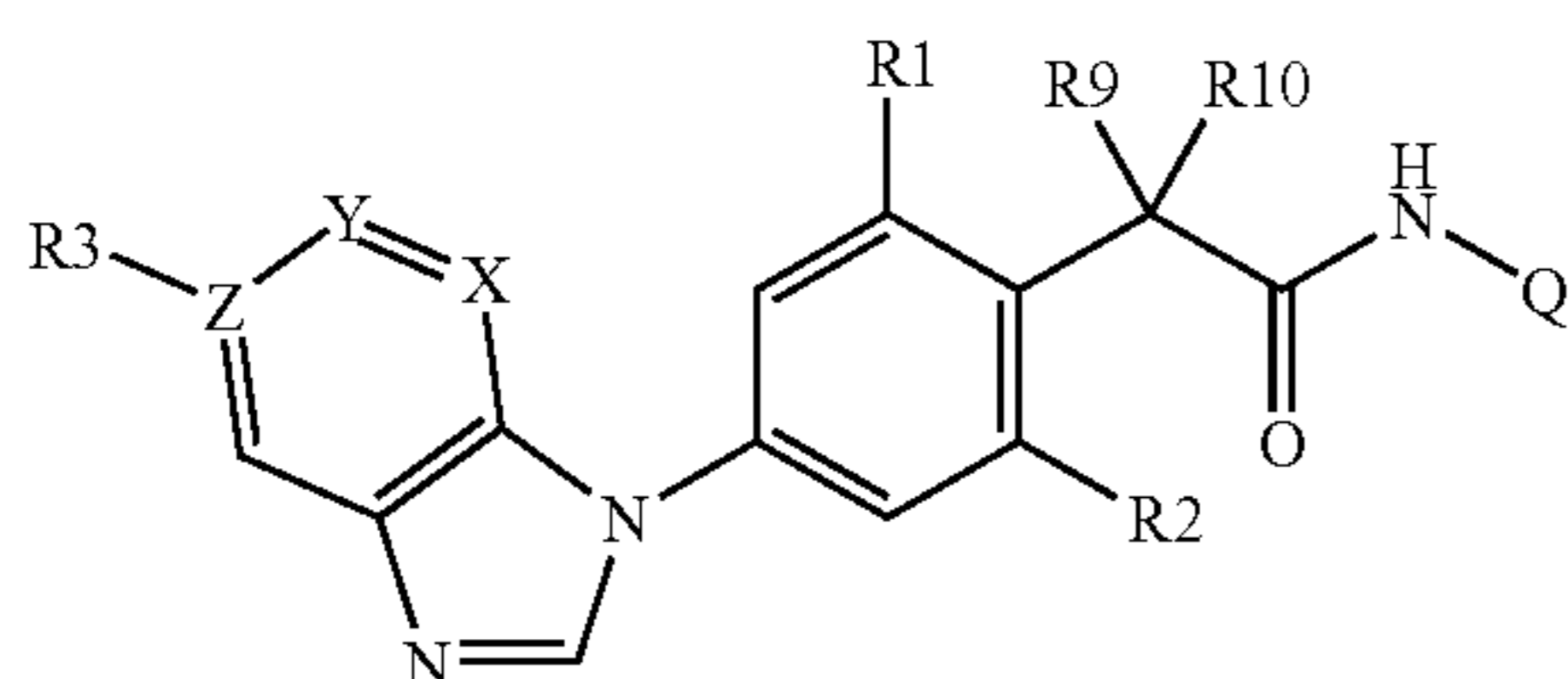
Capsules, comprising, as active ingredient, 100 mg of any one of the compounds of Examples 1 to 46, of the following composition are prepared according to standard procedures:

Composition	
Active Ingredient	100 mg
Avicel	200 mg
PVPPXL	15 mg
Aerosil	2 mg
magnesium stearate	1.5 mg
	318.5 mg

Manufacturing is done by mixing the components and filling them into hard gelatine capsules, size 1.

The invention claimed is:

1. A compound of formula (I)



wherein

(i) each of R1 and R2, independently of the other, is selected from the group consisting of hydrogen, halo and C₁-C₇alkyl;

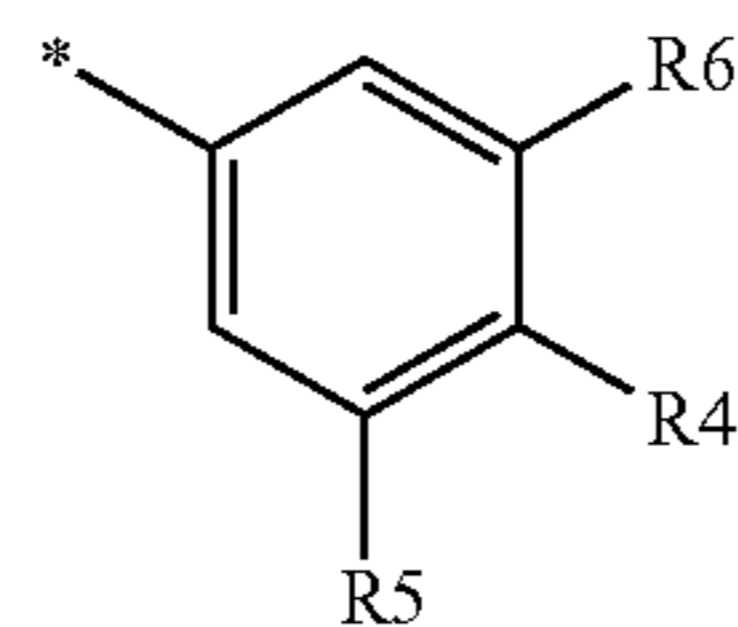
60

R3 is absent if Z is nitrogen or, if Z is C (carbon), is hydrogen, unsubstituted or substituted aryl or unsubstituted or substituted heterocyclyl;

X is N (nitrogen) or CH (hydrogen-substituted carbon), Y is CH or N,

Z is C or N, and

Q is a group of the formula (A)



wherein

(a) R4 is hydrogen, halo, unsubstituted or substituted amino, unsubstituted or substituted aryl, unsubstituted or substituted heterocyclyl bound via a ring atom other than nitrogen, unsubstituted or substituted cycloalkyl, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl or unsubstituted or substituted alkynyl; R5 is 1-methyl-piperidin-4-yloxy, 1-methyl-piperidin-4-yl, 2-dimethylamino-ethyl or 4-ethyl-piperazin-1-yl; and

R6 is hydrogen, unsubstituted or substituted cycloalkyl or unsubstituted or substituted alkyl; or

(b) R4 is 1-methyl-piperidin-4-ylmethyl, 1-ethyl-piperidin-4-ylmethyl, 1-methyl-piperidin-4-yloxy or 1-isopropyl-piperidin-4-ylmethyl;

R5 is hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted amino, unsubstituted or substituted aryl or unsubstituted or substituted heterocyclyl; and

R6 is hydrogen, unsubstituted or substituted cycloalkyl or unsubstituted or substituted alkyl;

where the asterisk * in formula (A) marks the bond through which the moiety is bound to the NH of the amide group in formula (I); and

either each of R9 and R10, independently of the other, is selected from the group consisting of hydrogen, hydroxyl and C₁-C₇-alkyl; or

R9 and R10 together represent oxo; or

R1 and R9 together form a group —C(O)—CH₂— or —CH₂—CH₂—, R2 is selected from the group consisting of hydrogen, halo and C₁-C₇-alkyl, and R10 represents hydrogen; or a salt thereof;

or

(ii) which is selected from the group consisting of

2-(4-Benzoimidazol-1-yl-phenyl)-N-[4-(4-isopropyl-piperazin-1-ylmethyl)-3-trifluoromethyl-phenyl]-acetamide,

2-(4-Benzoimidazol-1-yl-phenyl)-N-(4-diethylaminomethyl-3-trifluoromethyl-phenyl)-acetamide),

2-(4-Benzoimidazol-1-yl-phenyl)-N-(4-pyrrolidin-1-ylmethyl-3-trifluoromethyl-phenyl)-acetamide,

2-(2-Chloro-4-imidazo[4,5-b]pyridin-3-yl-phenyl)-N-(4-diethylaminomethyl-3-trifluoromethyl-phenyl)-acetamide,

2-(2-Chloro-4-imidazo[4,5-b]pyridin-3-yl-phenyl)-N-(4-pyrrolidin-1-ylmethyl-3-trifluoromethyl-phenyl)-acetamide,

N-[3-(4-Ethyl-piperazin-1-ylmethyl)-5-trifluoromethyl-phenyl]-2-(4-imidazo[4,5-b]pyridin-3-yl-phenyl)-acetamide,

61

N-(3-Diethylaminomethyl-5-trifluoromethyl-phenyl)-2-(4-imidazo[4,5-b]pyridin-3-yl-phenyl)-acetamide, 2-(4-Benzoimidazol-1-yl-phenyl)-N-(3-diethylaminomethyl-5-trifluoromethyl-phenyl)-acetamide, 2-(4-Imidazo[4,5-b]pyridin-3-yl-phenyl)-N-[3-(4-methyl-imidazol-1-yl)-5-trifluoromethyl-phenyl]-acetamide, 2-(4-Imidazo[4,5-b]pyridin-3-yl-2-methyl-phenyl)-N-[3-(4-methyl-imidazol-1-yl)-5-trifluoromethyl-phenyl]-acetamide, 2-(4-Imidazo[4,5-b]pyridin-3-yl-2-methyl-phenyl)-N-[3-(4-methyl-piperazin-1-yl)-5-trifluoromethyl-phenyl]-acetamide, N-[3-(4-Ethyl-piperazin-1-ylmethyl)-5-trifluoromethyl-phenyl]-2-(4-imidazo[4,5-b]pyridin-3-yl-2-methyl-phenyl)-acetamide, 2-(2-Chloro-4-imidazo[4,5-b]pyridin-3-yl-phenyl)-N-[3-(4-methyl-imidazol-1-yl)-5-trifluoromethyl-phenyl]-acetamide, 2-(4-Benzoimidazol-1-yl-phenyl)-N-[3-(4-methyl-imidazol-1-yl)-5-trifluoromethyl-phenyl]-acetamide, 2-(4-Benzoimidazol-1-yl-phenyl)-N-[3-(4-ethyl-piperazin-1-ylmethyl)-5-trifluoromethyl-phenyl]-acetamide, and 2-(4-Imidazo[4,5-b]pyridin-3-yl-2-methyl-phenyl)-N-[4-(1-methyl-piperidin-4-ylmethyl)-3-trifluoromethyl-phenyl]-acetamide; or a salt thereof.

2. A compound of formula I according to claim 1 selected from

N-[3-(4-Ethyl-piperazin-1-yl)-phenyl]-2-(4-imidazo[4,5-b]pyridin-3-yl-phenyl)-acetamide, 2-(4-Benzoimidazol-1-yl-phenyl)-N-[4-(4-isopropyl-piperazin-1-ylmethyl)-3-trifluoromethyl-phenyl]-acetamide, 2-(4-Imidazo[4,5-b]pyridin-3-yl-phenyl)-N-[4-(1-methyl-piperidin-4-ylmethyl)-3-trifluoromethyl-phenyl]-acetamide, 2-(4-Benzoimidazol-1-yl-phenyl)-N-(4-diethylaminomethyl-3-trifluoromethyl-phenyl)-acetamide, 2-(4-Benzoimidazol-1-yl-phenyl)-N-(4-pyrrolidin-1-ylmethyl-3-trifluoromethyl-phenyl)-acetamide, 2-(2-Chloro-4-imidazo[4,5-b]pyridin-3-yl-phenyl)-N-(4-diethylaminomethyl-3-trifluoromethyl-phenyl)-acetamide, 2-(2-Chloro-4-imidazo[4,5-b]pyridin-3-yl-phenyl)-N-(4-pyrrolidin-1-ylmethyl-3-trifluoromethyl-phenyl)-acetamide, N-[3-(4-Ethyl-piperazin-1-ylmethyl)-5-trifluoromethyl-phenyl]-2-(4-imidazo[4,5-b]pyridin-3-yl-phenyl)-acetamide, N-(3-Diethylaminomethyl-5-trifluoromethyl-phenyl)-2-(4-imidazo[4,5-b]pyridin-3-yl-phenyl)-acetamide, 2-(4-Benzoimidazol-1-yl-phenyl)-N-(3-diethylaminomethyl-5-trifluoromethyl-phenyl)-acetamide, N-[4-(1-Ethyl-piperidin-4-ylmethyl)-3-trifluoromethyl-phenyl]-2-(4-imidazo[4,5-b]pyridin-3-yl-phenyl)-acetamide, 2-(4-Benzoimidazol-1-yl-phenyl)-N-[4]-ethyl-piperidin-4-ylmethyl)-3-trifluoromethyl-phenyl]-acetamide, 2-(2-Chloro-4-imidazo[4,5-b]pyridin-3-yl-phenyl)-N-[4-(1-ethyl-piperidin-4-ylmethyl)-3-trifluoromethyl-phenyl]-acetamide, 2-(2-Chloro-4-imidazo[4,5-b]pyridin-3-yl-phenyl)-N-[4-(1-isopropyl-piperidin-4-ylmethyl)-3-trifluoromethyl-phenyl]-acetamide,

62

2-(4-Imidazo[4,5-b]pyridin-3-yl-phenyl)-N-[4-(1-isopropyl-piperidin-4-ylmethyl)-3-trifluoromethyl-phenyl]-acetamide, 2-(4-Benzoimidazol-1-yl-phenyl)-N-[4-(1-isopropyl-piperidin-4-ylmethyl)-3-trifluoromethyl-phenyl]-acetamide, 2-(2-Chloro-4-imidazo[4,5-b]pyridin-3-yl-phenyl)-N-[4-(1-methyl-piperidin-4-ylmethyl)-3-trifluoromethyl-phenyl]-acetamide, 2-(4-Benzoimidazol-1-yl-phenyl)-N-[4-(1-methyl-piperidin-4-ylmethyl)-3-trifluoromethyl-phenyl]-acetamide, 2-(4-Imidazo[4,5-b]pyridin-3-yl-phenyl)-N-[3-(4-methyl-imidazol-1-yl)-5-trifluoromethyl-phenyl]-acetamide, 2-(4-imidazo[4,5-b]pyridin-3-yl-2-methyl-phenyl)-N-[3-(4-methyl-imidazol-1-yl)-5-trifluoromethyl-phenyl]-acetamide, 2-(4-Imidazo[4,5-b]pyridin-3-yl-2-methyl-phenyl)-N-[3-(4-methyl-piperazin-1-yl)-5-trifluoromethyl-phenyl]-acetamide, N-[3-(4-Ethyl-piperazin-1-ylmethyl)-5-trifluoromethyl-phenyl]-2-(4-imidazo[4,5-b]pyridin-3-yl-2-methyl-phenyl)-acetamide, 2-(2-Chloro-4-imidazo[4,5-b]pyridin-3-yl-phenyl)-N-[3-(4-methyl-imidazol-1-yl)-5-trifluoromethyl-phenyl]-acetamide, 2-(4-Benzoimidazol-1-yl-phenyl)-N-[3-(4-methyl-imidazol-1-yl)-5-trifluoromethyl-phenyl]-acetamide, 2-(4-Benzoimidazol-1-yl-phenyl)-N-[3-(4-ethyl-piperazin-1-ylmethyl)-5-trifluoromethyl-phenyl]-acetamide, 2-(4-Imidazo[4,5-b]pyridin-3-yl-2-methyl-phenyl)-N-[4-(1-methyl-piperidin-4-ylmethyl)-3-trifluoromethyl-phenyl]-acetamide, 2-(2-Chloro-4-imidazo[4,5-b]pyridin-3-yl-phenyl)-N-[3-[(2-dimethylamino-ethyl)-methyl-amino]-5-trifluoromethyl-phenyl]-acetamide, N-[3-[(2-Dimethylamino-ethyl)-methyl-amino]-5-trifluoromethyl-phenyl]-2-(4-imidazo[4,5-b]pyridin-3-yl-2-methyl-phenyl)-acetamide, N-[3-[(2-Dimethylamino-ethyl)-methyl-amino]-5-trifluoromethyl-phenyl]-2-(4-imidazo[4,5-b]pyridin-3-yl-phenyl)-acetamide, 2-(4-Benzoimidazol-1-yl-phenyl)-N-[3-[(2-dimethylamino-ethyl)-methyl-amino]-5-trifluoromethyl-phenyl]-acetamide, 2-(4-Benzoimidazol-1-yl-phenyl)-N-[4-(1-methyl-piperidin-4-yloxy)-3-trifluoromethyl-phenyl]-acetamide, 2-(4-Imidazo[4,5-b]pyridin-3-yl-phenyl)-N-[4-(1-methyl-piperidin-4-yloxy)-3-trifluoromethyl-phenyl]-acetamide, 2-(4-Imidazo[4,5-b]pyridin-3-yl-2-methyl-phenyl)-N-[4-(1-methyl-piperidin-4-yloxy)-3-trifluoromethyl-phenyl]-acetamide, 2-(2-Chloro-4-imidazo[4,5-b]pyridin-3-yl-phenyl)-N-[4-(1-methyl-piperidin-4-yloxy)-3-trifluoromethyl-phenyl]-acetamide, 2-(2-Chloro-4-imidazo[4,5-b]pyridin-3-yl-phenyl)-N-[3-[methyl-(1-methyl-piperidin-4-yl)-amino]-5-trifluoromethyl-phenyl]-acetamide, 2-(4-Imidazo[4,5-b]pyridin-3-yl-2-methyl-phenyl)-N-[3-[methyl-(1-methyl-piperidin-4-yl)-amino]-5-trifluoromethyl-phenyl]-acetamide, 2-(4-Imidazo[4,5-b]pyridin-3-yl-phenyl)-N-[3-[methyl-(1-methyl-piperidin-4-yl)-amino]-5-trifluoromethyl-phenyl]-acetamide,

63

2-(4-Benzoimidazol-1-yl-phenyl)-N-[3-[methyl-(1-methyl-piperidin-4-yl)-amino]-5-trifluoromethyl-phenyl]-acetamide,
2-(2-Chloro-4-imidazo[4,5-b]pyridin-3-yl-phenyl)-N-[3-(1-methyl-piperidin-4-yloxy)-5-trifluoromethyl-phenyl]-acetamide,
2-(4-Imidazo[4,5-b]pyridin-3-yl-2-methyl-phenyl)-N-[3-(1-methyl-piperidin-4-yloxy)-5-trifluoromethyl-phenyl]-acetamide,
2-(4-Imidazo[4,5-b]pyridin-3-yl-phenyl)-N-[3-(1-methyl-piperidin-4-yloxy)-5-trifluoromethyl-phenyl]acetamide, and

64

2-(4-Benzoimidazol-1-yl-phenyl)-N-[3-(1-methyl-piperidin-4-yloxy)-5-trifluoromethyl-phenyl]-acetamide; or a salt thereof.

5 **3.** A compound of claim **1** in the form of a pharmaceutically acceptable salt.

4. A pharmaceutical composition comprising a compound of claim **1** in association with at least one pharmaceutically acceptable excipient.

10

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